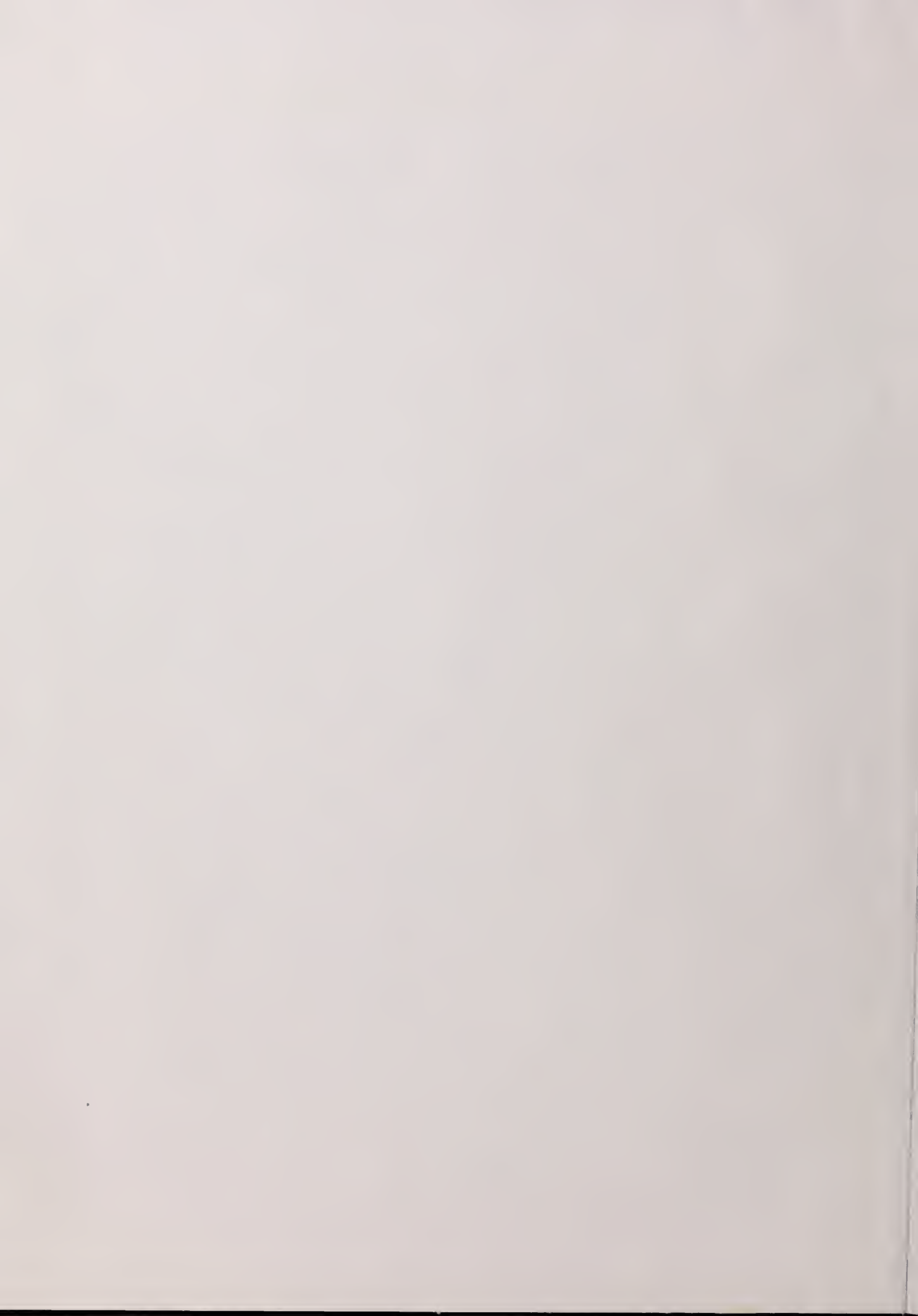


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VOL. 76 / NUM. 7

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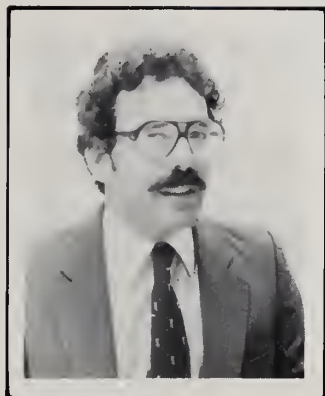
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Columna del Editor



En este número cabe destacar la publicación de un estudio clínico con relación al tratamiento de reacciones de rechazo en los pacientes de trasplante. La experiencia local en este sentido ha sido idéntica a la de los autores que informan su experiencia en un Centro de Trasplante en Michigan, EE UU. Con la utilización del suero antilinfocítico en el manejo de los episodios de rechazo se ha logrado disminuir marcadamente la mortalidad y el uso de prednisona en estos casos. Es una observación importante y muy apropiada en estos tiempos donde cada día se efectúan más trasplantes de cadáveres.

Aparece por primera vez la sección titulada: Objetivos de Salud para los Estados Unidos en 1990 y su aplicación a Puerto Rico. El artículo "Vigilancia y Control de Enfermedades Infecciosas" es el primero de una serie de quince que serán publicados en los próximos dos o tres años. Estos artículos cubrirán todos los temas de las metas nacionales de salud y serán preparados por el Dr. José G. Rigau, Director de la División de Epidemiología del Departamento de Salud y miembro de nuestra Junta Editora. Su contenido e implicaciones se supone tengan una relevancia significativa en las directrices futuras de la Salud Pública en nuestra isla. El Boletín de la Asociación Médica de Puerto Rico se las presenta a sus lectores.

Rafael Villavicencio, MD, FACC
Presidente Junta Editora
Boletín Asociación Médica de Puerto Rico

ASOCIACIÓN MÉDICA DE PUERTO RICO BOLETÍN



VOL. 76 / NUM. 7 JULIO 1984

NUESTRA PORTADA:

"La Finca del Barrio Guaraguo" de Francisco Oller

Este óleo del más grande de los artistas puertorriqueños es el segundo de una serie de Oller que engalanan la portada de nuestro Boletín.

Francisco Manuel Oller y Cestero nació en San Juan el 17 de junio de 1833 cerca de donde es hoy el Parque de las Palomas. Su talento artístico se reconoció temprano, desde su adolescencia comenzó a pintar en las iglesias de la isla con su primer maestro, Juan Cleto Noa. A los 14 completa su primera pintura: una reproducción de un óleo de su abuelo, el Dr. Francisco Oller, que había sido pintado por José Campeche. A los 18 años se traslada a España donde estudia pintura con Federico Madrazo por dos años. Al regresar a Puerto Rico en 1853 permanece por 5 años, expone sus obras, gana numerosos premios y su éxito lo lleva a París en 1858 en busca de nuevos conocimientos. París fue un punto culminante en la vida de Oller donde estudió, compartió, y fue influenciado por los grandes maestros de la época.

Oller fue un liberal del siglo 19 que se opuso a la esclavitud, abogó por los derechos de las minorías y confió en que Puerto Rico desarrollaría una sociedad e instituciones públicas libres y progresistas.

La Finca del Barrio Guaraguo fue realizada en 1875. Es una pintura paisajista de gran calidad donde se aprecia el efecto de la sombra y la luz creada por el sol tropical así como el verdor de la vegetación nuestra.

Por desgracia para nuestra sociedad y nuestro patrimonio artístico esta obra fue hurtada del Ateneo Puertorriqueño en 1980 junto con otras dos ("Ramón Power" y "El Pintor Campeche") de gran valor, y que pertenecían a la colección Oller del Ateneo. Hasta el día de hoy no se sabe de estas obras, se piensa que pueden estar fuera de Puerto Rico.

La reproducción de esta obra en nuestra portada ha sido posible gracias a la gentileza de la señora Emma Boehm-Oller, nieta del pintor y Presidenta de "The Oller Collection Inc.", con sede en Nueva York. El Boletín de la Asociación Médica de Puerto Rico se honra con esta portada.

EDITORIAL



T.E.F.R.A., H.C.F.A., P.P.S., D.R.G., H.B.P., etc., etc.

En agosto 19 de 1982 el Congreso aprobó la ley llamada TEFRA (Tax Equity & Fiscal Responsibility Act) que además de contener medidas relacionadas con aumentos en impuestos y con una reforma tributiva contienen numerosas provisiones que afectan a los Programas de Medicare y Medicaid. La Legislación traerá los cambios más significativos en Medicare desde su concepción en 1965. Las implicaciones económicas se cree llegarán a reducir los gastos de Medicare y Medicaid en más de 14 billones de dólares en tres años.

TEFRA ha tenido un gran impacto en los hospitales porque modifica la manera en que se reembolsa al Hospital sus gastos. La ley provee al secretario de HHS (Health & Human Resources) a través de HCFA (Health Care Financial Administration) de la creación de los mecanismos sobre los cuales los costos de proveer cuidado médico en hospitales y otras instituciones.

P.P.S. (Prospective Pay System)

Bajo el viejo sistema de reembolso el hospital recibía los gastos auditados que fueran razonables proveyendo otros renglones como capital, educación, y ajustes laborales que bajo el nuevo sistema serán en gran parte eliminadas o modificadas con una rebaja en el reembolso que el hospital va a recibir o está recibiendo en los Estados en que ya está implementada.

H.B.P. (Hospital Based Physicians)

La ley provee al Secretario de HHS a establecer reglas para distinguir entre servicios médicos cubiertos por Parte A que envolvían cuidado directo a pacientes en general del hospital o de una facilidad de enfermería especializada. Según la ley los servicios médicos profesionales son sólo aquellos que llenan los siguientes requisitos y serán cubiertos por Parte B.

- a) son servicios rendidos personalmente a un paciente en particular por el médico
- b) son servicios que contribuyen al diagnóstico o al tratamiento del paciente en particular
- c) ningún otro profesional le puede brindar estos servicios al paciente. Los servicios profesionales cubiertos bajo parte A se están reembolsando siempre y cuando sean razonables y no exceda los RCE (Reasonable Compensation Equivalent).

R.C.E. (Reasonable Compensation Equivalent)

Fue desarrollada por HCFA como parte de la misma ley para compensar "razonablemente" los servicios que los médicos prestan a los pacientes en general dentro de un hospital (HBP) y están cubiertos por Parte A. Las cifras que se escogieron como razonables están basadas en una labor completa de 2,080 horas anuales 1 (FTE) - Full Time Equivalent. FTE y las cantidades son sacadas de el promedio reportado en los últimos cuatro años como los ingresos promedios en las diferentes especialidades. A estas cifras se les hacen modificaciones dependiendo si el hospital está en una zona metropolitana de más de 1 millón de habitantes o está en una metrópolis de menos de millón o si es rural o urbana. Así se establecen compensaciones que fluctúan entre \$90,000.00 en una cantidad de más de 1 millón de habitantes en la zona metropolitana hasta un radiólogo con \$123,000. El resto de las especialidades caen dentro de esos límites.

Para que esos servicios sean pagados tienen que haber unas constancias por escrito ante el intermediario, las horas que ese médico invierte en ese trabajo so pena de suspensión de pagos o contrato con Medicare para el médico y el hospital si hay engaño en el reporte.

Estas regulaciones están ya en efecto desde octubre 1983 pero al implementarse el sistema de PPS desaparecerán por no ser necesario.

P.P.S. - Prospective Pay System

En abril 20 de 1983 el Presidente de los Estados Unidos firmó la ley 98-21 que se conoce como la ley de enmiendas al seguro social. El título sexto de esta ley provee que el pago de Medicare a los hospitales por los servicios a los pacientes hospitalizados será a base de un sistema de pagos prospectivo (PPS) en lugar del sistema antiguo de costo reembolsable. Bajo esta ley el pago será a base de un precio específico predeterminado por cada paciente dado de alta de la institución. Los hospitales tendrán que funcionar dentro de esos pagos determinados por el gobierno federal por tipo de diagnóstico.

El compuesto de pago prospectivo para cada hospital toma en consideración factores como: diagnóstico principal, tamaño del hospital, localización, fecha en que el hospital termina su año fiscal económico, costo del año base, etc. Entre los factores que intervienen y que nos

afectan grandemente a Puerto Rico es que el Medicare divide a la nación en 9 regiones y cada región lo subdivide entre la zona rural y la zona urbana.

Cada región y cada zona tiene una diferente connotación económica de tal suerte que el factor económico por el cual se multiplica el diagnóstico es diferente según la región de Estados Unidos donde esté el hospital. Puerto Rico y los otros territorios de Estados Unidos han sido excluidos de el pago prospectivo por creer Medicare que como los costos laborales de Puerto Rico son más bajos que en Estados Unidos el incluir a los hospitales de Puerto Rico sería un factor que bajaría en algo los costos de los hospitales en los Estados Unidos.

D.R.G.s - (Diagnostic Related Groups)

El sistema de clasificación DRG fue desarrollado en la Universidad de Yale usando 1.4 millones de expedientes médicos de los cuales clasificaron 400,000 en 23 MDCs (Categorías Diagnósticos Mayores).

Cada MDC representa una categoría clínica que se diferencia de los otros por el sistema orgánico afectado y por la causa de las diferentes enfermedades. Estas 23 categorías fueron divididas en sub-grupos hasta llegar a 470 categorías llamadas "Diagnosis Related Groups" (DRGs).

Para efectos de reembolso cada diagnóstico tiene un pago prospectivamente determinado, es decir, el precio se establece por adelantado para el diagnóstico principal.

Diagnóstico principal es aquel que luego que el paciente ha sido estudiado completamente se determinó la necesidad de la admisión de ese paciente. El diagnóstico de admisión no va a ser siempre el diagnóstico principal.

Los DRGs no reflejan directamente la etapa o la severidad de la enfermedad de un paciente de tal modo que dos pacientes en el mismo DRG puede consumir recursos muy dispares. Recientemente se ha establecido un nuevo método para clasificar cada enfermedad o problema médico en etapas o estadios según la severidad (excluyendo la muerte.)

Estadio I - Condición sin complicaciones o problemas con severidad mínima.

Estadio II - Condición con complicaciones locales o severidad moderada.

Estadio III - Condición con complicaciones sistémicas o problema con severidad.

Esta clasificación puede aplicarse a pacientes con problemas médicos o quirúrgicos con una o más etiología y las tres estadios se pueden subdividir en más categorías.

Etc., Etc.

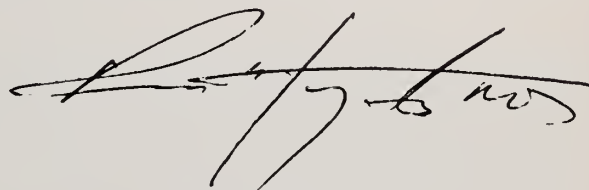
La pregunta que todo el mundo se hace es si el cuidado médico será de la misma calidad dentro de este sistema de pagos prospectivo y de grupos de diagnóstico.

No hay una contestación que pueda tener toda la certeza que pedimos las partes envueltas en los problemas de la salud; a saber: los pacientes, los médicos, el gobierno y las compañías aseguradoras. Pero si es meridianamente claro el hecho que los hospitales que bajo este sistema sobrevivirán serán aquellos en que su Facultad Médica,

administración y todo el personal constituyan un equipo con unidad de destino y de propósito. Donde el quehacer se haga de la manera más eficiente, más económica y basada en la premisa que cada parte del equipo está obrando de la mejor buena fe y al máximo de sus capacidades y conocimientos pensando en la manera como el paciente va a recibir el mejor tratamiento posible dentro de las posibilidades.

Los médicos tenemos la responsabilidad de velar porque las condiciones del hospital donde se trabaja sean los más apropiados para el descargo de nuestras responsabilidades y que todos los miembros de la Facultad Médica practiquen el mismo tipo de medicina eficiente que incluye: admisiones justificadas, el uso apropiado de los recursos disponibles, el tener al día los expedientes médicos, la apropiada codificación, la participación en Comités de la Facultad y el acatar decisiones de esos comités que como el de Utilización, Garantía de Calidad, y Farmacia agilizan el cuidado médico.

Para algunos esto será pedirnos demasiado pero será la participación militante de los médicos en los problemas de la práctica médica los que evitarán el que algún día pueda cambiar el rol que por derecho los médicos tenemos en los problemas de la salud de nuestros pacientes.

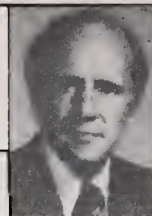


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Presidente Sección Neumología
Asociación Médica de Puerto Rico



MEDICAL DIRECTOR'S PAGE

Bruce H. Medd, M.D., Assistant Vice President and Director,
Professional and Marketing Services



Recognizing the Manipulative Patient

Use of illicit drugs plus misuse of some important prescription medications (particularly those with central nervous system effects) increase the possibility that sooner or later most primary care physicians will be confronted with the problem of identifying and dealing with the drug-seeking patient. Whether encountered in a private practice, a clinic setting, a neighborhood health center, a busy emergency room, a rural area or a large metropolitan hospital, these patients can generally be identified by their use of one or more of the following four manipulative approaches;^{1,2} they...

- **ASSUME PHYSICAL PROBLEMS**—particularly illnesses having symptoms of severe pain (such as renal colic, toothache or tic douloureux) which are generally treated with narcotic medications
- **FEIGN PSYCHOLOGICAL PROBLEMS**—complaining of insomnia, fatigue, depression and anxiety when stimulants or depressants rather than analgesics are the medicines desired
- **USE DECEPTION**—employing theft, forgery or alteration of prescriptions, concealing or pretending to take medications and requesting refills prematurely (often with the excuse that the medicine was "lost" or "stolen") to obtain additional supplies
- **EMPLOY COERCIVE TACTICS**—attempting to elicit sympathy or guilt feelings in the physician, using direct threats of physical or financial harm, bribery or citing influential families or friends to obtain the medications they desire.

In addition, physicians should be alert to certain common mannerisms exhibited by these individuals.

Common Behavioral Characteristics of the Drug-Seeking Patient

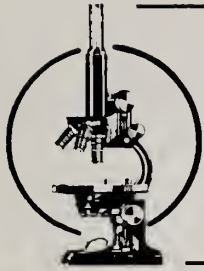
- Present dramatic but vague complaints
- Present subjective complaints without confirming objective signs
- Present a self-diagnosis and request specific medication
- Exhibit no interest in confirming a diagnosis or undertaking other forms of treatment
- Exhibit lack of interest in keeping appointments for referrals or diagnostic tests

The pressure these individuals can bring to bear on a physician can be considerable; however, medical experts have suggested that when encountering such a patient, physicians maintain a strong professional control of the situation and regard the patient as having a serious illness.¹ Referral to a specialized treatment program may also be required in some cases.^{2,3}

References: 1. Wilford BB: Prescribing practices and drug abuse, chap. 10, in *Drug Abuse: A Guide for the Primary Care Physician*. Chicago, American Medical Association, 1981, pp. 263-284. 2. *Ibid.* Screening for drug abuse in a general patient population, chap. 5, pp. 113-122. 3. Nightingale SL, DuPont RL: Drug abuse and role of physicians, chap. 4, in *Drug Abuse—Clinical and Basic Aspects*, edited by Pradhan SN, Dutta SN, St. Louis, CV Mosby Co., 1977, pp. 37-45.

If you would like to receive additional information on identifying and dealing with the manipulative/medication-abusing patient, ask your Roche representative or write to me: Bruce H. Medd, M.D., Assistant Vice President and Director, Professional and Marketing Services.

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PATHOLOGY *Review*

María Castillo-Staab, M.D.

Un niño de 10 años de edad es admitido al hospital en fallo cardíaco congestivo severo presentando edema de las piernas, dificultad para respirar, hepatomegalia y dolor en el pecho.

Su enfermedad dió comienzo tres meses atrás con dolor de garganta y fiebre, seguido semanas más tarde, de dolores en las piernas, palidez, pérdida de apetito y dificultad para respirar. Al momento de la admisión la radiografía del pecho mostró cardiomegalia. El electrocardiograma reveló alteraciones del segmento ST y prolongación del segmento PR.

El paciente falleció dos días después de la admisión. La autopsia reveló cardiomegalia y lesiones en el miocardio y endocardio similares a las que se ilustran a continuación.

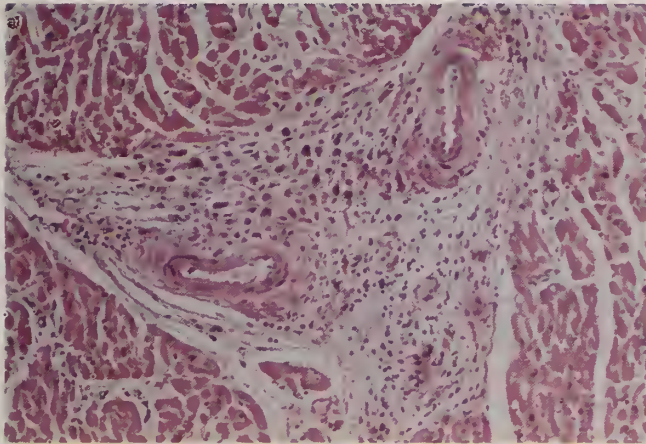


Fig. 1. Lesión intramiocárdica perivascular.

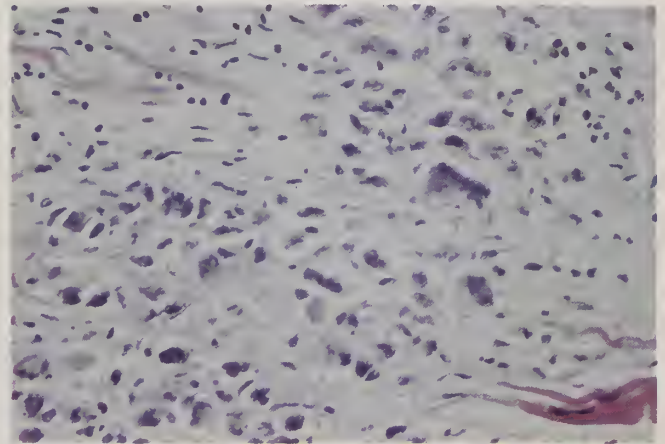


Fig. 2. Células grandes algunas multinucleadas en las fibras colágenas del tejido conjuntivo.

¿Cuál es su diagnóstico?

- A. Fiebre reumática aguda; nódulo de Aschoff.
- B. Sífilis congénita; guma.
- C. Miocarditis tuberculosa.
- D. Artritis reumatoidea, variedad juvenil.
- E. Histoplasmosis.

Fiebre Reumática Aguda - Nódulo de Aschoff

El nódulo de Aschoff es la lesión histológica que caracteriza el proceso inflamatorio de la fiebre reumática. Aunque se encuentran clásicamente en los tejidos cardíacos, lesiones parecidas pueden encontrarse en las bolsas sinoviales, tendones, membranas serosas y el tejido celular subcutáneo. El daño tisular básico en fiebre reumática ocurre en las fibras colágenas del tejido conectivo. Los nódulos de Aschoff representan lesiones algo granulomatosas que consisten en un foco central de fibras colágenas hinchadas y alteradas (necrosis fibrinoide), rodeadas por células blancas mononucleares, fibroblastos y células grandes mesenquimales modificadas llamadas células de Anitschkow. Se ven también células gigantes multinucleadas llamadas células de Aschoff.

En el corazón, los nódulos de Aschoff se localizan en el estroma del miocardio, alrededor de los vasos intramiocárdicos, en el endocardio valvular y en la grasa subepicárdica.

La fiebre reumática aguda sigue presente en Puerto Rico y esta posibilidad diagnóstica debe descartarse siempre que nos enfrentemos a un niño o niña de edad escolar con signos de fallo cardíaco congestivo.

La fiebre reumática aguda es una enfermedad sistémica inflamatoria que ocurre luego de una infección de la garganta causada por cepas de estreptococo grupo A, beta-hemolítico. La patogenia es algo complicada y la teoría más aceptada apunta hacia una reacción inmunológica entre productos del estreptococo que se fijan a ciertos tejidos como el corazón y anticuerpos producidos por el paciente en contra de estos antígenos. Algunos de estos antígenos presentan reacción cruzada con el sarcolema de las fibras miocárdicas.

El daño tisular provocado por esta reacción no se limita a las fibras miocárdicas sino que también afecta a otros tejidos mesenquimales y al endotelio vascular.

Además de la carditis reumática los pacientes pueden presentar poliartritis migratoria, eritema marginatum, nódulos subcutáneos y corea de Sydeham. Los criterios diagnósticos de Jones se basan en estos hallazgos. Aunque la incidencia de fiebre reumática ha declinado, en parte debido al uso preventivo de la penicilina, la carditis reumática continúa representando un problema clínico en ciertas poblaciones y constituye un factor etiológico importante en el desarrollo de enfermedad cardíaca valvular.

La carditis reumática ocurre en el 30% de los pacientes con fiebre reumática aguda. Está caracterizada por un proceso inflamatorio no supurado que envuelve una o todas las capas del corazón.

Cuando todas las capas del corazón (endocardio, miocardio y pericardio) están envueltas hablamos de pancarditis. Las lesiones en el endocardio valvular provocan alteraciones en la estructura de sostén de las valvas que al repararse eventualmente con fibrosis, vascularización y calcificación, deforman las válvulas lo suficientemente como para producir estenosis y/o regurgitación.

Este proceso es de larga duración y es el resultado de infecciones repetidas, muchas insidiosas, que pasan inadvertidas para el paciente.

La miocarditis reumática es una manifestación de la fase aguda de la carditis reumática.

El corazón aparece aumentado de tamaño con dilatación. El miocardio es pálido y blando. Microscópicamente los nódulos de Aschoff se encuentran en el tejido conectivo intersticial del miocardio y aparentemente su presencia contribuye a los hallazgos electrocardiográficos de prolongación del intervalo PR, bloqueo atrioventricular de primer grado y disminución del voltaje del complejo Q R S.

Las manifestaciones clínicas de fallo congestivo cardíaco en fiebre reumática aguda se deben en la mayoría de los casos a miocarditis severa.

Referencias

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Successful

Too preoccupied on business trips to remember his pills.

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Loves kids...his wife would like several more.

Impotent

Blames his current blood pressure medication.



Patient description is a hypothetical composite based on clinical experience and evaluation of data.

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and virtually
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TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol) with caution—see OVERDOSAGE. Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyroidosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.5%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (4%-1%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agnucytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nor-epinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted by the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on file, Stuart Pharmaceuticals. 2. Herman RL, Lamdin E, Fischetti JL, Ko HK. Postmarketing evaluation of atenolol (Tenormin®): A new cardioselective beta-blocker. *Curr Ther Res* 1983; 33(1):165-171. 3. Zacharias FJ. Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980; 6 (suppl 1):86-89.



STUART PHARMACEUTICALS

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Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Sexual dysfunction rare

Only 0.4% of the patients in the evaluation reported sexual performance problems²—making TENORMIN an excellent choice for men like Manuel G, who may have become impotent on other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

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The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



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STUART PHARMACEUTICALS

ESTUDIOS CLINICOS

Treatment of Multiple Rejection Episodes with ALG or ATGAM After Cadaveric Renal Transplantation

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Abstract: The clinical experience described in this report indicates that ALG or ATGAM can be safely used as initial prophylactic treatment followed by ALG or ATGAM antirejection therapy for multiple rejection episodes. In general, application of this protocol to a patient population where half of the patients were considered to be at high risk for transplantation resulted in improved graft and patient survival, and less morbidity than our previous experience using steroid therapy on a similar patient population.

Since the introduction of antilymphocyte and antithymocyte preparations as biologic immunosuppressants over a decade ago, these drugs have been widely evaluated for use in clinical renal transplantation.^{1, 2} The use of ALG and ATG as adjunctive therapy along with steroids immediately after transplantation has generally resulted in a 10-15% improvement in long-term graft survival and fewer rejection episodes as compared with steroid treated controls.^{1, 2} However, limited group size in many studies has made a statistical significant difference difficult to obtain, and well-controlled randomized studies have been less frequently reported. Another use of ALG and ATG has been for the treatment of rejection.³⁻²⁰ In this application, these drugs are generally considered to be highly effective for the treatment of first rejection episodes.^{1, 2} Reversal of rejection occurs more frequently and more rapidly with ALG and ATG than with steroids alone.^{1, 2} For the treatment of first rejection episodes ALG and ATG have been used either alone, as adjunctive therapy with steroids, or as sequential therapy (in steroid resistant rejection episodes).³⁻²⁰ There have been only a few

reports, however, where ALG or ATG have been used both prophylactically and as antirejection therapy.^{19, 20} Our present study reports on the effectiveness and safety of ALG and ATGAM in the treatment of three or more renal allograft rejection episodes after an initial prophylactic immunosuppressive course of ALG or ATG with low dose steroids.

Materials and Methods

The post-transplant course of 132 patients receiving cadaveric kidney grafts at our center, between October 1979 and October 1982, was assessed. Within this group of transplant recipients, 42 patients were treated for three or more rejection episodes with either antilymphoblast globulin (ALG, University of Minnesota) or antithymocyte globulin (ATGAM, Upjohn). The post-transplant morbidity and mortality of this group of patients was assessed to evaluate the safety and efficacy of this antirejection therapy in the treatment of multiple rejection episodes.

The study group was comprised of 29 males and 13 females ranging in age from 19 to 58 years old (mean = 36.28 + 10.44 years); 15 patients were older than 40. Ten of the 42 recipients were Type I diabetics. Twenty-one of the 42 recipients had two major risk factors, one major and two intermediate risk factors, or one intermediate and two or three minor risk factors, as previously defined for our transplant population.^{10, 22}

All recipients were followed between three and 39 months after transplantation (mean time after transplant = 17.4 months). One patient was transplanted with a second cadaver graft and the other 41 patients were transplanted with primary cadaver kidney grafts. The majority (>60 percent) of the patients received two or more blood transfusions prior to transplantation. Less than 40 percent had ≤ 10 percent preformed cytotoxic antibodies. (Organs were procured through the organ sharing program of the Organ Procurement Agency of Michigan.)

The majority of the patients received kidneys with a 1 or 0 HLA-AB tissue antigen match with the cadaver donor. Operative techniques remained constant through-

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out this period. The mean warm ischemia time for the donor kidneys was 4.95 ± 4.25 minutes and the mean preservation time for the entire group of kidneys was 24.69 ± 10.63 hours. Thirty-nine of the donor kidneys were preserved by hypothermic pulsatile perfusion with either plasma protein fraction (PPF, Plasmanate) (37 kidneys), PPF and 5% albumin (one kidney), or silica gel fraction (SGF) (1 kidney) for an average of 24.88 ± 10.13 hours. The three remaining kidneys were hypothermically stored in TP-II solution (a hyperosmolar SGF base colloid preparation)²¹ for an average preservation time of 25.6 ± 18.21 hours.

A standardized prophylactic immunosuppressive regimen was followed for all patients. Azathioprine was given just prior to surgery and on the first postoperative day at a dose of 2.0-5.0 mg/Kg/day, tapered to a maintenance dose of 1.0 to 0.75 mg/Kg/day, and adjusted to maintain the WBC count at 5.0×10^3 . Prednisolone was started just before surgery at 1 mg/Kg/day and rapidly tapered to a maintenance dose of 20-25 mg/day by three to four weeks posttransplantation. Equine or caprine ALG (38 patients) or ATGAM (4 patients) was administered prophylactically at an ideal dose of up to 20 mg/Kg/day, starting on the first postoperative day and continuing for 14 days. The amount of ALG or ATGAM varied from 10-20 mg/Kg/day adjusted to maintain the platelet count above 100,000.

The diagnosis of rejection was established by a sustained increase in serum creatinine >0.3 mg/dl above the previous stable value in any given day. Supportive findings included a decrease in urinary output volume (>25 percent), weight gain (>5 pounds), swelling of the renal graft, fever (≥ 100 F) and an increase in the kidney size confirmed by ultrasonography. More than two of these findings were always present at the time of the diagnosis of rejection and the institution of antirejection therapy.

Thirty eight patients in the study group were treated for rejection with ALG and four patients were treated with ATGAM, at a dose of 10-20 mg/Kg/day for 10 days for first and second rejection episodes. Third rejection episodes were treated with the same dosage for 5-10 days. Intermittent ALG or ATGAM at 10 mg/Kg/day was given every fourth to seventh day for the fourth and subsequent rejection episodes depending on the change in the serum creatinine level and the patient's general condition. In general, patients received 30-40 gm of ALG or ATGAM during the periodic intermittent antirejection treatment. No additional prednisolone therapy was given beyond the maintenance dose of 20-25 mg/day for any rejection episodes.

Calculations of graft and patient survival were done using the actuarial method.²³

Results

Figure 1 displays the actuarial graft and patient survival for all of the patients in this series. One year actuarial graft survival for these patients was 87.4% and one year patient survival was 94.8%. Two-year actuarial values were 68.4 and 94.8% respectively. Table I details the graft and patient survival for the subgroups receiving ALG or ATGAM.

Successful reversal of chronic rejection episodes was evidenced by a decrease in serum creatine values back towards pre-rejection levels. However, the baseline serum creatinine level during the quiescent period between rejection episodes increased slightly with each subsequent rejection episode.

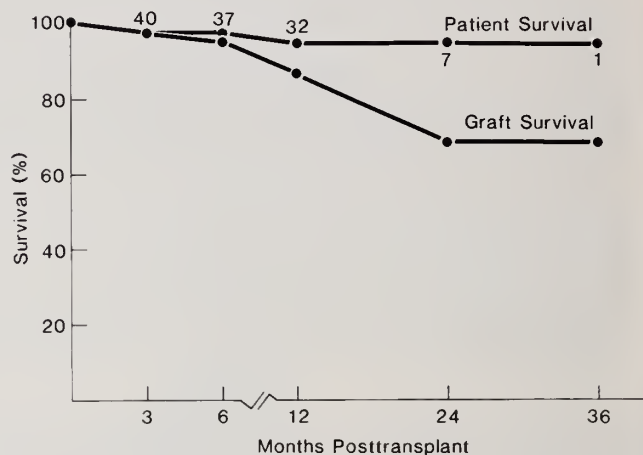


Figure 1. Actuarial patient and graft survival for renal transplant patients receiving ALG or ATGAM for the treatment of chronic rejection episodes. Numbers above each point indicate patients at risk at the end of each post-transplant interval.

TABLE I

Actuarial Graft and Patient Survival of Renal Allograft Recipients Treated for Multiple Rejection Episodes			
Combined ALG or ATGAM group (n=42)			
Time at risk	#Patients at risk at end of each interval	Graft Survival	Patient Survival
1 month	42	100%	100%
6 months	37	95.1%	97.5%
1 year	32	87.5%	94.8%
2 years	7	68.4%	94.8%
ALG group (n=38)			
Time at risk	#patients at risk at end of each interval	Graft Survival	Patient Survival
1 month	38	100%	100%
6 months	35	94.7%	97.4%
1 year	31	89.3%	97.4%
2 years	7	69.9%	97.4%

Every patient in the study group experienced fever and chills at least once out of multiple treatments. In order to minimize the collateral reactions observed after ALG or ATGAM administration, 50 mg diphenamine hydrochloride (Benadryl, Parke-Davis) was given orally or intramuscularly and 40 mg hydrocortisone sodium succinate (Solu-cortef, Upjohn) was administered intra-

muscularly immediately prior to the administration of the ALG or ATGAM. Several patients (7 of 42, 16.6%) demonstrating allergic reactions to equine ALG were switched the caprine ALG preparation. No malignancies were observed after long-term ALG or ATGAM administration.

A low incidence of infection was again observed^{10, 16, 19} using ALG/ATG to treat multiple rejection episodes. In fact only two deaths, in this series, were due to infection. One was due to a persistent urinary tract infection associated with diabetic visceral neuropathy which eventually caused septicemia in a patient that received a combined kidney and pancreas transplant. The other death was due to hypoglycemia and alcoholism.

Two renal grafts were lost due to the previously mentioned deaths. Five kidney grafts were removed due to irreversible rejection between 5 and 22 months after transplantation. One kidney transplant was removed because of an infection which occurred after the patient underwent an abortion.

Discussion

Although the adjunctive application of ALG and ATG remains controversial, multiple trials have shown that the application of these preparations to primary cadaveric kidney transplantation can result in a 10-15% improvement in graft survival for 1-2 years, without significant changes in patient survival.^{1, 2} It appears that early rejection episodes may be more easily reversed and that the onset of the first rejection episode is also delayed using these adjunctive immunosuppressive agents.^{1, 2} In addition, no increased incidence of infection or tumor has been observed in these patients.

ALG and ATG preparations have also been used for the treatment of first rejection episodes, as adjunctive therapy, as separate therapy and as sequential after initial use of steroids.³⁻¹⁸ In these applications ALG and ATG are generally considered to be effective and their use is associated with better long-term graft survival than standard rejection therapy.¹⁻¹⁸ In addition, some centers have observed that second rejection episodes are less frequent after ALG and ATG therapy. The combined use of ALG or ATGAM as both prophylactic and antirejection therapy with low dose maintenance steroids has been reported by one center²⁰ other than our own.^{10, 16, 19} However, we have been the only trial which has applied prophylactic ALG or ATGAM with ALG or ATGAM antirejection therapy, without increasing steroids for multiple rejection episodes.

In our initial trial, ALG was used for the treatment of chronic rejection episodes after initial prophylactic use in a group of recipients who were assessed to be at high risk for cadaveric renal transplantation.²² Application of our immunosuppressive protocol allowed for successful treatment of rejection without an accompanying increase in oral steroids beyond low maintenance levels. This contrasted with our previous experience with a similar high risk transplant population, using a standard steroid immunosuppressive protocol, which was associated with increased morbidity and poor patient survival.¹⁰

Our present study includes a larger number of patients

and substantiates our previous evaluation of this protocol.¹⁹ We realize that these data are not the result of a prospective randomized comparison of ALG or ATGAM and another immunosuppressive protocol, however, our previous disappointing experience with the standard steroid therapy on a similar group of patients at the same center serves as baseline from which we have significantly improved. A prospective randomized study with well matched groups of patients would possibly be useful in determining the exact percent increase that may be obtained using ALG or ATGAM in this manner. However, we are encouraged by this preliminary evaluation and feel that the benefits of this immunosuppressive protocol should offset the increased cost of using long-term ALG and ATGAM for the treatment of chronic rejection after renal transplantation. Again, we observed a low incidence of infection using ALG or ATGAM for the treatment of multiple (≥ 3) rejection episodes. This was comparable to studies reported by others who have found either no difference or a decrease in the infection rate when steroid and ALG/ATG treated groups are compared.¹⁻²⁰ Only one patient, in our series, receiving ALG or ATGAM in our current study, died as a result of an infection, and one graft was lost in this patient population due to an infection which occurred after the patient received an abortion.

Resumen: Nuestra experiencia clínica descrita en este reporte indica que el ALG o ATGAM pueden usarse prácticamente sin riesgo importante como terapia profiláctica y subsecuentemente para el tratamiento de múltiples episodios de rechazo. En general, la aplicación de nuestro protocolo, a una población alta de pacientes de riesgo elevado, resultó en una mejoría definitiva en la sobrevida del paciente y del injerto con menos morbilidad de la que hemos visto en pacientes en los cuales hemos utilizado esteroides previamente.

Acknowledgement

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Read this like your life depends on it.

Breast cancer found early and treated promptly has an excellent chance for cure. About a week after your period, practice this self-examination.



1. In bath or shower.

Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.

Comparative Evaluation of Three Methods for Measuring Gentamicin in Serum

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Abstract: Three methods for measuring gentamicin levels in serum were compared: radioimmunoassay (RIA), enzyme multiplied immunoassay test (EMIT), and latex agglutination inhibition card test (Latex). There was a high degree of correlation among the methods. RIA was the least expensive test when the number of samples measured was 12. EMIT was the least time consuming method but the most expensive. Latex was the least expensive method for 1 and 6 samples. The method to be employed by a particular laboratory will depend on the number of samples to be tested, cost considerations and personnel time available.

There are several methods for measuring gentamicin concentration in body fluids, among them the microbiological assay, the enzymatic method using an adenylating enzyme, and radioimmunoassay.¹⁻³ The choice among procedures depends on the size and workload of the institution and the cost and practicality of the method. For large institutions, radio immunoassay is the most commonly used test. In recent years, rapid methods for measurements of aminoglycosides have appeared.⁴⁻⁷ The purpose of this study is to compare two new methods, the enzyme multiplied immunoassay test (EMIT) and the latex agglutination inhibition card test (Latex) with the long-established radioimmunoassay test (RIA). These three methods were compared to determine the degree of correlation, the ease of implementation and the cost difference among them.

Materials and Methods

Assay systems.

Radioimmunoassay. The RIA method is based on competition between ¹²⁵I-labeled gentamicin and non-radioactive antibiotic for a limited number of antibody sites. The amount of radioactivity measured in the resulting complex is inversely proportional to the amount of antibiotic in the sample. The RIA-NEN (New England Nuclear Corp., Boston, Mass.) method for gentamicin was used as a representative test of RIA because it is the

one available at our institution. It consists of a 100 or a 500 test kit, containing six standards and internal control sera, containing gentamicin 3.2 and 12.8 micro g/ml, respectively. Tests were performed as directed in the instruction manual supplied with each kit. Assays by RIA were done in duplicate and counted in a Gamma 7000 counter (Beckman Instruments, Fullerton, Ca.). The average of duplicate scintillation counts was used to produce a standard curve, using samples containing 0, 1, 2, 4, 8 and 16 ug of gentamicin per ml. The percentage of maximum binding of ¹²⁵I was plotted on the Y-axis, and gentamicin concentration on the X-axis of semilogarithmic graph paper, and the results of specimens were calculated from the graph by using the mean value of counts.

EMIT method. The enzyme multiplied immunoassay test (Syva Corp., Palo Alto, Calif.) is based on competitive binding, using an enzyme as a label and an antibody as the specific-binding protein. The amount of free gentamicin in the test sample competes with enzyme-labeled drug for antibody sites. The more gentamicin present in the serum, the more aminoglycoside complex is free to act on the substrate. Sera were analyzed for gentamicin following the manufacturer's instructions using a Gilford Stasar III (Gilford Instrument Lab., Inc., Oberlin, Ohio) microsample spectrophotometer equipped with a thermally regulated flow cell. The standards were 1, 2, 4, 8 and 16 ug of gentamicin per ml. Specimens were diluted with a pipetter-diluter. The absorbance of the standards was automatically fed into a Syva CP-5000 clinical processor, and the standard-curve data were automatically calculated. The EMIT control sample (6 micro g/ml) was tested before each run.

Latex agglutination inhibition card test. The Macrovue Gentamicin Card Test (Hynson, Westcott and Dunning, Baltimore, Maryland) is a quantitative latex agglutination inhibition test designed to measure the concentration of serum gentamicin. Gentamicin sensitized latex particles react with anti-gentamicin antisera. The addition of serum containing gentamicin inhibits the agglutination reaction. According to instructions provided with the kit, the patient's serum was diluted with buffer directly on the indicated circle of a black plastic coated card. The serum dilutions were 1:2, 1:3, 1:4, 1:5, 1:6, 1:8, 1:10, 1:12, 1:16, 1:20, 1:24, and 1:32. Four standard concentrations of gentamicin (0.3, 0.4, 0.5 and 0.6 micro g/ml), were also placed on the test card at their indicated positions. A 0.025 ml amount of anti-

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gentamicin antiserum was added to each serum dilution and to each standard concentration and mixed. One drop of latex antigen suspension containing a specific concentration of a gentamicin latex conjugate was added, and the card containing the mixtures was mechanically rotated for 9 min. The concentration of gentamicin in the serum specimen was determined by multiplying the reciprocal of the highest dilution of serum that inhibited the agglutination reaction by the lowest concentration of gentamicin standard which showed similar inhibition.

Analyses of clinical samples. Forty-two serum samples were obtained from patients at the San Juan Veterans Administration Hospital who were receiving gentamicin as the only antibiotic therapy. Most samples were obtained immediately, before, and 1 hour after IV antibiotic administration. Serum samples from every patient were divided into aliquots, and kept frozen at -80°C for up to a maximum of three weeks until assayed. Aliquots for each one of the 42 samples were unfrozen, and assayed simultaneously by the three methods. Other aliquots of 10 serum samples (two samples from each of five patients) were assayed simultaneously and daily for 5 days to determine the reproducibility of the method. The means of the gentamicin concentration in duplicate assays in every single system were used for comparison by the linear regression analysis, where the correlation coefficient and *p* value were determined.⁸ The coefficient of variation (CV) was calculated in the standard manner by dividing the standard deviation by the mean and multiplying by 100.⁸ Control samples were run with each system.

Results

The range, mean and standard deviation of the 42 samples tested by the 3 methods are presented in Table I. There were no statistically significant differences in the mean values of 3.18 micro g/ml for RIA, 2.90 micro g/ml for EMIT and 3.25 micro g/ml for the Latex methods.

TABLE I

Results of three assay measurements of gentamicin in 42 consecutive samples		
Assay*	Range micro (g/ml)	Mean \pm SD \pm micro (g/ml)
RIA	0.02 - 15.5	3.18 \pm 2.67
EMIT	< 0.5 - 11.0	2.90 \pm 2.30
Latex	< 1 - 14.8	3.25 \pm 0.50

*RIA, Radioimmunoassay; EMIT, enzyme multiplied immunoassay test; Latex, latex agglutination inhibition card test.

†SD, Standard deviation

In Figure 1, the linear correlations for the 3 methods obtained by linear regression analysis are presented, demonstrating a high degree of correlation with *r* values ranging from 0.97 to 0.99. Upon comparison with the conventional RIA method of gentamicin assay, both the EMIT and Latex methods yield a high correlation ($p \leq 0.001$). Table III indicates the coefficient of varia-

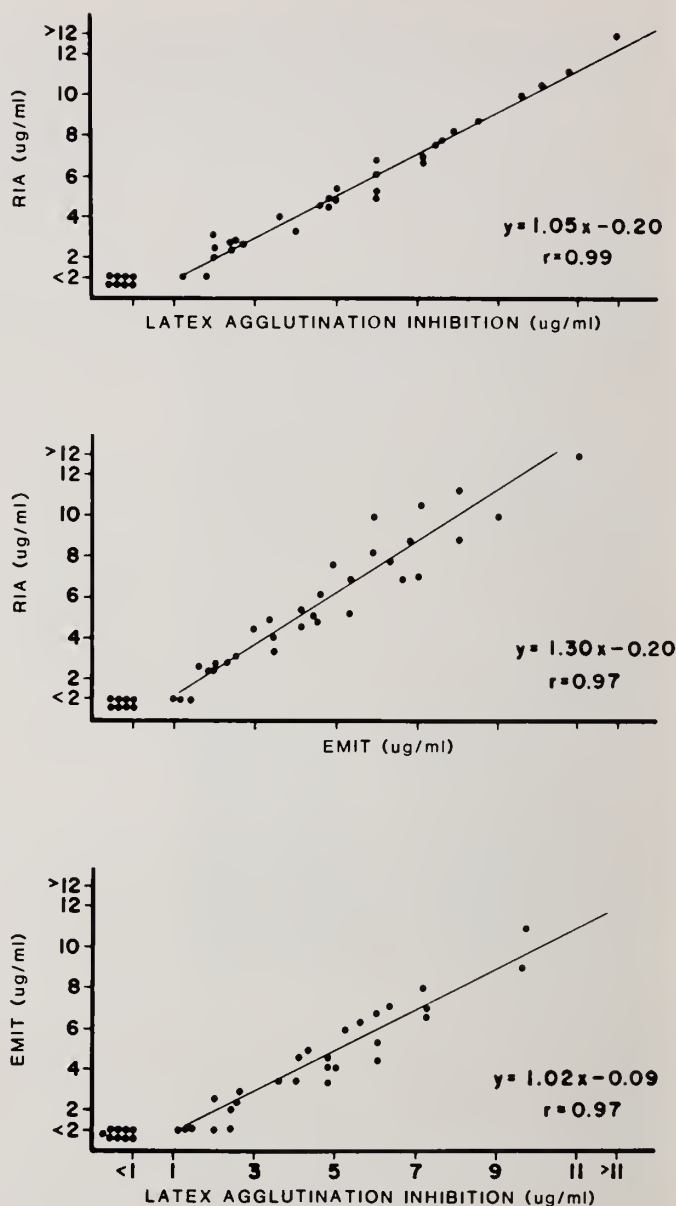


Figure 1. Correlation (linear regression analyses) of gentamicin values obtained with the RIA, EMIT, and Latex agglutination inhibition card systems for 42 clinical samples.

tion, mean and range obtained for the three assays when gentamicin levels were determined daily on five separate days in 10 serum specimens. The mean serum gentamicin concentrations by the three assays is similar as shown in the Table. The coefficient of variation for samples containing greater than 2 micro g/ml was less than 12% (0.68, 11.8, 2.3, 8.6, 0.73 and 2) for the latex agglutination inhibition card test, compared with less than 9% (3.2, 0, 8.3, 1.6, 4.8 and 0.1) for the corresponding samples assayed by RIA and less than 5% (0.77, 0.96, 2.4, 1.9, 4.2 and 0) for the EMIT. For samples containing 2 micro g/ml or less, the coefficient of variation for the Latex test was less than 6%, less than 9% for RIA, and less than 12% for EMIT.

TABLE II

Mean concentration, range and coefficient of variation (CV) obtained by three assays when gentamicin levels were determined for 10 serum specimens assayed on each of five days									
ASSAY									
Patient	Mean ug/ml	RIA* Range ug/ml	CV (%)	Mean ug/ml	EMIT* Range ug/ml	CV (%)	Mean ug/ml	LATEX* Range ug/ml	CV (%)
1	6.9	(6.6-7.2)	3.2	6.5	6.5-6.6)	0.77	7.3	(7.2-7.3)	0.68
1	2.4	(2.4-2.4)	0	1.8	(1.7-1.8)	2.8	2.0	(2-2)	0
2	5.4	(4.8-6.0)	8.3	5.2	(5.2-5.3)	0.96	6	(5-7)	11.8
2	0.03	(0.02-0.04)	0.3	< 0.5	(<0.5- <0.5)	NA†	<1	(<1- <1)	NA†
3	4.9	(4.8-5.0)	1.6	3.3	(3.2-3.4)	2.4	4.8	(4.6-4.9)	2.3
3	1.3	(1.1-1.4)	8.5	0.9	(0.8-1.1)	12	1.2	(1.1-1.3)	5.8
4	6.9	(6.4-7.2)	4.8	5.2	(5.1-5.3)	1.9	6.4	(6-7)	8.6
4	0.56	(0.33-0.8)	0.3	0.8	(0.8-0.8)	0	<1	(<1- <1)	NA†
5	10.5	(10-11)	4.8	9	(8.6-9.5)	4.2	9.6	(9.5-9.70)	0.73
5	2.8	(2.5-3.0)	0.1	2.3	(2.3-2.3)	0	2.5	(2.5-2.6)	2

*RIA, Radioimmunoassay; EMIT, enzyme multiplied immunoassay test; Latex, latex agglutination inhibition card test.

†NA, not applicable

Comparative cost and time analyses for the three assays are presented in Table III. The time required to perform the latex agglutination inhibition assay when gentamicin was measured in one specimen was 13 min. compared with 60 min. for the RIA and 15 min. for the EMIT. For 12 serum specimens the EMIT could be performed faster than both the RIA and latex agglutination inhibition assay (48 min. versus 84 min.).

Analyses of the cost of the assay materials as a function of the number of serum samples processed in a single batch indicate that the Latex test (\$4.00) was less expensive than RIA (\$15.06) and EMIT (\$23.86) when a single specimen is processed. For processing six specimens, the RIA test (\$4.63) per test) was slightly higher than Latex (\$4.00) and the most expensive was the EMIT test (\$7.33 per test). For 12 or more specimens, RIA was the least expensive of the three assay techniques.

results of our study with the EMIT system are similar to those of Ngui-Yen et al (1981) and those with the Latex agglutination inhibition card test are similar to those of Standiford et al (1981).^{5, 7}

In addition to accuracy and reproducibility, particular attention was paid to the cost involved. The latex agglutination system required very little disposable supplies, followed by EMIT system and by RIA system. Specimens assayed singly by the EMIT and RIA systems were more costly than the latex agglutination system. The final cost per assay based on 12 analyses was less expensive by the RIA method, followed by Latex and EMIT.

Although this study demonstrated differences among the costs of the test from the three systems, it is important to note that these costs, as quoted by competing suppliers, will vary considerably from time to time and from

TABLE III

Time and cost analysis for each of the three assay procedures for gentamicin in serum when 1, 6, and 12 specimens are processed daily							
Assay	Cost per sample for:*			Time per sample (min.) for:			Total time (min.) for:
	(No. of specimens)			(No. of specimens)			(No. of specimens)
	1	6	12	1	6	12	6 12
RIA†	\$15.06	\$4.63	\$3.59	60	12	7	72 84
EMIT†	23.86	7.33	5.69	15	7	4	42 48
Latex†	4.00	4.00	4.00	13	9	7	54 84

*Cost include only the purchase price of the assays and do not include labor and capital equipment, scintillation counters, microsample spectrophotometer, etc.

†RIA, Radioimmunoassay; EMIT, enzyme multiplied immunoassay test; Latex, latex agglutination inhibition card test.

Discussion

Comparative evaluation of the three systems in this study indicates that all three methods gave accurate and reproducible results. The RIA system required the most technical time per test because of the need to separate free antigen from bound antigen by centrifugation. The

place to place.

The high degree of correlation obtained between the three commercial kits for gentamicin quantitation suggests that any of the three methods can be used for routine serum analysis. Each clinical laboratory will determine the method to be used depending on its needs, volume of specimens and cost.

Resumen: Se compararon tres métodos para medir la concentración de gentamicina en suero: radioinmunoensayo (RIA), prueba múltiple de inmunoensayo enzimático (EMIT) y la prueba de tarjeta para la inhibición de la aglutinación de las partículas de latex (Latex). Se encontró un alto grado de correlación entre los métodos estudiados. RIA resultó la prueba menos costosa cuando el número de muestras que se procesaban era de 12. EMIT fue el método que menos tiempo consumió, pero fue el más costoso. Latex fue el método menos costoso cuando el número de muestras procesadas era de 1 y de 6. El método a emplearse por un laboratorio particular dependerá del número de muestras que tengan que analizarse, del presupuesto disponible y del tiempo con que cuente el personal para el análisis de las muestras.

Acknowledgment

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SIRVIENDO AL PUEBLO Y A LA PROFESION MEDICA



ASOCIACION MEDICA DE PUERTO RICO



LOS OBJETIVOS DE SALUD PARA ESTADOS UNIDOS EN 1990 Y SU APLICACION A PUERTO RICO.

I. Vigilancia y Control de Enfermedades Infecciosas

José G. Rigau Pérez, M.D., FAAP*

Resumen: En 1980 el Servicio de Salud Pública de los Estados Unidos publicó unas metas para el mejoramiento de la salud de los habitantes del país en los diez años siguientes. De las once metas nacionales de salud para 1990 referentes a la vigilancia y control de enfermedades infecciosas, ocho están bajo estudio y/o siendo perseguidas localmente, y tres necesitan trabajarse desde el plano más básico. La obtención de estos objetivos en Puerto Rico, al igual que en otros estados, exige la cooperación de diversas instituciones gubernamentales, académicas y cívicas. Futuros artículos discutirán las metas nacionales referentes a otras áreas de la salud.

En 1980 el Servicio de Salud Pública de los Estados Unidos ("U.S. Public Health Service") publicó unas metas para el mejoramiento de la salud de los habitantes del país en los diez años siguientes.¹ Quince asuntos prioritarios fueron identificados: control de la hipertensión, planificación familiar, embarazos y salud infantil, inmunizaciones, enfermedades transmitidas sexualmente, control de agentes tóxicos, seguridad y salud ocupacional, prevención de accidentes y control de traumatismos, fluorización y salud dental, vigilancia y control de enfermedades infecciosas, fumar y el deterioro en la salud, abuso de alcohol y drogas, nutrición, condicionamiento físico y ejercicio, control de la tensión y el comportamiento violento. Dentro de cada área se especificaron los objetivos a alcanzar para 1990. Estos objetivos (226 en total), planteados de manera mensurable, se desarrollaron en consultoría con más de 500 expertos de los sectores público y privado, que representaban agencias de salud federales, estatales y locales, grupos de consumidores, organizaciones de voluntarios y profesionales de salud. Las metas se establecieron tomando en cuenta las tendencias actuales de factores pertinentes,

tales como cambios demográficos estilos de vida y la disponibilidad de fondos, y detallando lo que se asumió ocurriría con estos factores en la década de 1980 a 1990. Las metas han de alcanzarse por los esfuerzos de toda la gama de agencias e instituciones públicas y privadas, de personas y comunidades, y no se han establecido como una responsabilidad federal. El gobierno federal se ve llamado a dirigir, catalizar y respaldar un esfuerzo colectivo con móviles locales, y lleva a cabo evaluaciones periódicas del progreso hacia estos objetivos.²⁻⁵

Este artículo presenta la situación actual en Puerto Rico respecto a cada uno de los objetivos relacionados con la vigilancia y control de las enfermedades infecciosas. El trabajo pretende establecer un mapa del terreno, para que sucesivas incursiones puedan ir mejor dirigidas a su destino. Mediante la preparación y presentación de estas estadísticas de salud se busca reconocer la severidad de los problemas estudiados, precisar qué datos hay disponibles, evaluar la consistencia y exactitud de las fuentes de información, señalar las acciones tomadas y sugerir opciones.

Métodos

Las metas aquí reseñadas fueron traducidas por el autor y se citan, en comillas, tal como aparecen en el texto original en inglés.¹ Los estimados de incidencia mencionados como parte de la cita se refieren siempre a los Estados Unidos. Se ha conservado, como en el original, el término "vacuna" para significar inmunización activa, aunque ninguno de los objetivos esté relacionado con la vacunación contra viruela. Cada meta se rotuló "AA", "P", o "I" de acuerdo con los siguientes criterios: AA (aparentemente alcanzada) si la evidencia (tal y como está disponible) indica que el estado de la enfermedad (o de la técnica de salud pública) al momento actual en Puerto Rico concuerda con lo deseado para 1990; P (perseguida) si hay al momento un esfuerzo de recolección de datos respecto al problema y/o un programa establecido para el control de la enfermedad o para prestación del servicio; I (indocumentada) si la información específica que estipula el objetivo no se conoce para Puerto Rico. Los datos de población se obtuvieron de la División de

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Recursos Humanos, Área de Planificación Económica y Social, de la Junta de Planificación de Puerto Rico, e indican el tamaño estimado de la población de Puerto Rico al primero de julio de cada año estudiado (1973 a 1982). Los datos de morbilidad provienen del Programa de Control de Enfermedades Transmisibles (hoy División de Epidemiología) de la Secretaría Auxiliar para Mantenimiento de la Salud (SAMS) del Departamento de Salud. La excepción la constituyen las estadísticas de tuberculosis, provenientes del Programa de Control de Tuberculosis de SAMS. Nuevos criterios para el diagnóstico de tuberculosis se empezaron a usar en 1975, y nuevas guías para el reporte de casos se implantaron en 1982. Las cifras de morbilidad están presentadas por año calendario. Las tasas de morbilidad (por 100,000 habitantes) están calculadas usando la población total de Puerto Rico, excepto para la tuberculosis en jóvenes de edad menor de 15 años (en que se utilizó la cifra correspondiente a la población de ese grupo etario). Los datos de mortalidad se extrajeron de los análisis detallados inéditos que hace la Oficina de Estadísticas, Análisis y Control de Información (Administración de Facilidades y Servicios de Salud, Departamento de Salud) de los certificados de defunción que se cumplimentan cada año; los datos para 1982 no estaban disponibles al momento de esta investigación. Hasta 1978 se usó la octava edición de la "International Classification of Diseases, Adapted for use in the United States" (ICDA-8), para identificar por números las causas de muerte, cambiando en 1979 a la nueva edición (ICDA-9).^{6, 7} Las rúbricas correspondientes a las enfermedades aquí estudiadas fueron las siguientes: tuberculosis- 010-19.9 (ICDA-8), 010-18.9 (ICDA-9); hepatitis (A y B)- 070 (ICDA-8), 070-70.9 (ICDA-9); meningitis bacteriana y no especificada- 320-320.9 (ICDA-8), 320-322.9 (ICDA-9); meningitis meningocócica- 036.0 (ICDA-8 y 9). Las tasas por enfermedad en Estados Unidos se tomaron del "Annual summary 1981: reported morbidity and mortality in the United States", informe disponible más reciente.⁸

Objetivos Para 1990

Mejoramiento del estado de salud

A. "Para 1990 la incidencia anual estimada de hepatitis B debe disminuirse a 20 por 100,000 habitantes. (En 1978 se estimaba en 45 por 100,000 habitantes.)" - P

La incidencia anual reportada de hepatitis B en Puerto Rico en 1982 fue 9.68 por 100,000 habitantes (tabla 1). Aunque la rúbrica para hepatitis como causa de muerte combina hepatitis A y B, se han utilizado estas cifras en la tabla 1 porque la hepatitis A es muy rara como causa de muerte.⁹ La meta para 1990 se refiere a una incidencia estimada, no a la incidencia reportada. Sería muy aventurado suponer que, dada la similaridad de las cifras de incidencia reportada en Puerto Rico y Estados Unidos, hay la misma similaridad en las cifras de incidencia estimada. No hay información sobre la incidencia anual estimada de hepatitis B en nuestra población, y solo hay dos estudios de la prevalencia de marcadores serológicos de infección por hepatitis B en grupos de la población de Puerto Rico. La tasa anual de positividad para antígeno

superficial de hepatitis B (HBsAg) en la sangre de donantes voluntarios asintomáticos examinados en el Centro de Sangre de la Cruz Roja Americana en Puerto Rico en los últimos 5 años (1 de julio de 1978 a 30 de junio de 1983), incluyendo personas de Puerto Rico e Islas Vírgenes ha variado de 0.9 a 3.8 casos positivos por mil donantes. La tasa promedio para todo el período es de 2.3 casos positivos para HBsAg por cada mil donantes.¹⁰ Esta tasa es casi idéntica a la reportada en 1977 para 499 muestras de Puerto Rico examinadas en los Laboratorios de Servicios de Sangre de la Cruz Roja en Maryland. En ese estudio, Puerto Rico resultó ser el país latinoamericano (de los estudiados) con la menor tasa de prevalencia de HBsAg en las muestras sometidas.¹¹ Las tasas en Puerto Rico son similares a las reportadas para países del norte de Europa.¹² Una encuesta serológica llevada a cabo entre personal y pacientes del Hospital de Veteranos de San Juan, determinó que en donantes de sangre, la tasa de prevalencia de anticuerpos contra HBsAg (anti-HBs) era 17%.¹³ Desgraciadamente, estos estudios en donantes de sangre no proporcionan la información necesaria para determinar la frecuencia y distribución de la hepatitis B en la población de Puerto Rico.

TABLA 1

Hepatitis B en Puerto Rico, 1973-82

Año	Muertes	Casos	Población total	Tasa de incidencia por 100,000 habitantes
1973	4	32	2,872,300	1.11
1974	4	23	2,890,000	.80
1975	8	50	2,938,800	1.70
1976	5	60	3,018,300	1.99
1977	9	42	3,074,100	1.37
1978	5	53	3,121,600	1.70
1979	6	94	3,160,700	2.97
1980	15	85	3,206,900	2.65
1981	14	169	3,246,800	5.21
1982		316	3,263,273	9.68

Tasa Estados Unidos 1981 9.22 (Incidencia estimada en 1978-45.00)

Meta Puerto Rico 1990 (Incidencia estimada) 20.00

El aumento en los casos de hepatitis B reportados anualmente en Puerto Rico en los últimos tres años puede tener varias causas, aunque ninguna de ellas se puede confirmar por las estadísticas a la mano. Es posible que la población esté teniendo una mayor exposición a los factores de riesgo para hepatitis B, como lo son las agujas mal esterilizadas. Sin embargo, también hay que considerar que el establecimiento de programas de control de infecciones intrahospitalarias (nosocomiales), y la popularización de las pruebas serológicas para hepatitis han facilitado la identificación y notificación de los casos de hepatitis B. Todavía no se ha afianzado en Puerto Rico el uso de la vacuna de virus inactivado de hepatitis B. Sería muy útil, para establecer prioridades para el uso de la vacuna, contar con estudios serológicos de prevalencia de HBsAg en diversos grupos ocupacionales y sociales, y especialmente en las embarazadas (por la necesidad de proteger con inmunoglobulina específica al recién nacido, si la madre es portadora de HBsAg).

B. "Para 1990 la incidencia anual reportada de tuberculosis debe disminuirse a 8 por 100,000 habitantes." (En 1982 era en Puerto Rico 14 por 100,000 habitantes.) Las metas nacionales para la planificación de salud redactadas en 1980 por la Administración de Recursos de Salud del Servicio de Salud Pública de Estados Unidos señalan también como objetivo reducir a cero la incidencia de tuberculosis en las personas menores de 15 años de edad.¹⁴ — P

La tasa anual de casos de tuberculosis en Puerto Rico (tabla 2) se ha mantenido estable desde 1976. La tasa de tuberculosis en personas menores de 15 años de edad (tabla 3) es inferior a la tasa de los Estados Unidos, pero todavía está por encima de la meta para 1990, que exige la eliminación de la enfermedad en este grupo etario. Sin embargo, la Asociación Americana del Pulmón acepta como su meta para 1990 que la tasa para niños menores de 5 años sea un caso por 100,000 habitantes (aunque su meta para la población general - 6 casos por 100,000 habitantes - es más ambiciosa que la meta que aquí presentamos).¹⁵ Un esfuerzo especial en la búsqueda de casos en 1980 en Puerto Rico casi duplicó el número de casos reportados sobre lo que se había notificado el año anterior, sugiriendo que la magnitud del problema de tuberculosis es posiblemente más del doble de lo que

TABLA II

Tuberculosis en Puerto Rico, 1973-82

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	256	519	18
1974	252	585	20
1975	236	551	19
1976	185	454	15
1977	198	419	14
1978	130	375	12
1979	139	437	14
1980	120	820	26
1981	92	553	17
1982		473	14
Tasa Estados Unidos 1981			12
Meta Puerto Rico 1990			8

TABLA III

Tuberculosis en personas de menos de 15 años de edad, en Puerto Rico, 1973-82

Año	Muertes	Casos	Tasa por 100,000 habitantes	Población ≤ 14 años
1973	1	31	3.02	1,027,500
1974	0	42	4.10	1,023,700
1975	3	34	3.27	1,038,600
1976	1	49	4.70	1,043,600
1977	2	22	2.13	1,033,600
1978	1	22	2.11	1,041,100
1979	1	21	2.07	1,014,300
1980	1	26	2.58	1,007,300
1981	1	16	1.65	972,300
1982		21	2.15	975,453
Tasa Estados Unidos 1981			3.28	
Meta Puerto Rico 1990			.00	

reflejan las estadísticas usuales de morbilidad. La disminución en tasas desde entonces puede deberse a dificultades en la detección de casos y búsqueda de contactos o a los estrictos requisitos para la definición de un caso que imponen las nuevas guías nacionales para la notificación de la enfermedad. Atendidas a los antiguos criterios (pre-1982), las cifras para 1982 hubieran incluido 175 casos más, haciendo un total de 648 casos, para una tasa de 20 casos por cien mil habitantes.

C. "Para 1990 la incidencia anual estimada de neumonía neumocócica debe disminuirse a 115 por 100,000 habitantes. (En 1978 se estimaba en 182 por 100,000 habitantes.)" — I

No hay estudios que midan la incidencia de pulmonía neumocócica en la población de Puerto Rico. Para alcanzar esta meta será necesario también precisar cuánto se usa la vacuna contra neumococos, y qué factores obstaculizan su uso en las personas a mayor riesgo de la enfermedad.

D. "Para 1990 la incidencia anual reportada de meningitis bacteriana debe disminuirse a 6 por 100,000 habitantes. (En 1978 se estimaba en 8.2 por 100,000 habitantes.)" — P

En Puerto Rico, a diferencia de muchos estados de la Unión Norteamericana la meningitis es una enfermedad de declaración obligatoria. Las tres categorías de diagnóstico a notificarse son la meningitis viral (aséptica), la meningitis meningocócica y la de otras causas. Las cifras de incidencia de meningitis bacteriana en Puerto Rico (tabla 4) incluyen, por lo tanto, las meningitis meningocócicas, las de otras causas bacterianas, las de causa no especificada, y un número desconocido de meningitis no bacterianas que se confunden con las bacterianas parcialmente tratadas o con cultivo negativo. El sistema de vigilancia de la enfermedad ha mejorado mucho desde 1978 gracias a la labor de vigilancia de las enfermeras epidemiólogas regionales y a la cooperación de los sistemas de control de infecciones nosocomiales. La fiabilidad de la información que ellos proveen sólo puede constatarse mediante la comparación de expedientes hospitalarios y las hojas de notificación de enfermedades que llegan a la División de Epidemiología (estudio que no

TABLA IV

Meningitis Bacteriana* y no especificada en Puerto Rico, 1973-1982

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	58	33	1.15
1974	72	30	1.04
1975	50	62	2.11
1976	64	70	2.32
1977	56	65	2.11
1978	47	168	5.38
1979	72	214	6.77
1980	50	263	8.20
1981	41	217	6.68
1982		204	6.25
Meta Puerto Rico 1990			6.00

*incluyendo meningocócica

se ha hecho). Sin embargo, es evidente que en 1973 y 1974 la notificación de casos era muy deficiente (morían más casos de los que se notificaban), y que desde 1978 el número de casos informados es mucho mayor que el de las muertes. El número de muertes por meningitis ha variado muy poco de 1973 a 1982, lo que indica que el aumento en casos reportados no se debe a mayor incidencia de la enfermedad (lo que haría aumentar el número de muertes), sino a mayor eficiencia en la notificación de casos.

E. "Para 1990 la incidencia (por factor específico de riesgo) de infecciones nosocomiales en hospitales de cuidado agudo debe disminuirse por un 20% de lo que sería en ausencia de un programa de control de infecciones. (En 1979 se estimó que 5% de todos los pacientes hospitalizados padecían infecciones nosocomiales, y la tasa general de infecciones adquiridas en el hospital parece estar aumentando, aunque no tanto en hospitales con buenos programas de control de infecciones.) Un porcentaje similar de reducción debe observarse en facilidades de cuidado prolongado y de cuidado residencial. (No hay datos de referencia disponibles.)" — P

Este objetivo señala que, por ejemplo, si la tasa de infecciones urinarias nosocomiales en pacientes con cateter uretral es 10% en un hospital sin programa de control de infecciones, se deben tomar medidas para que la tasa baje a por lo menos 8% (un 20% de reducción). No es lógico asignar recursos de un hospital para recoger estos datos de referencia en vez de dedicarlos a implantar un sistema de control de infecciones, por eso no hay datos de referencia disponibles. La mayoría de los hospitales en Puerto Rico tienen estos sistemas en funcionamiento desde 1978 (y algunos desde mucho antes), pero la información que recogen no ha sido publicada.

Mejoramiento en los servicios y la protección

F. "Para 1990 el 95% de las facilidades con licencia para el cuidado de pacientes deben aplicar las prácticas recomendadas para controlar infecciones nosocomiales. (No hay datos de referencia disponibles.)" — P

La mayoría de los hospitales de Puerto Rico tienen un programa de control de infecciones que se dedica a disseminar y enforzar las recomendaciones del comité de control de infecciones del hospital. No hay información publicada sobre la existencia de sistemas similares en facilidades no hospitalarias, tales como asilos de ancianos. Sería muy útil contar con una descripción de los programas existentes en la isla y con un análisis de las razones que favorecen o atrasan la formación de programas de control de infecciones en los hospitales.

G. "Para 1990 los sistemas de vigilancia epidemiológica y control deben ser capaces de responder a, y controlar: 1) enfermedades nuevas y epidemias inesperadas de importancia para la salud pública; 2) infecciones traídas del extranjero." — P

No es apropiado que el autor evalúe los trabajos y planes de su propia oficina. Cabe aquí, sin embargo, la descripción del sistema en vigor. La División de Epidemiología, ubicada desde el 2 de agosto de 1983 en la

Secretaría Auxiliar para Mantenimiento de la Salud del Departamento de Salud de Puerto Rico, es la agencia responsable de la recolección y análisis de los datos de las enfermedades de notificación obligatoria (tabla 5).¹⁶ El personal técnico de la División consiste de un epidemiólogo (el autor) y una enfermera, con oficinas en el Sótano del Edificio E, Hospital de Siquiatría, Centro Médico (Apartado 71423, Correo General de San Juan, PR 00936, teléfonos 758-5344, 758-5422). Siguiendo el sistema de regionalización vigente en el Departamento de Salud, la División de Epidemiología provee asesoramiento al personal regional (usualmente una enfermera epidemióloga regional) y evalúa las actuaciones de la Región en cuanto a la vigilancia y control de las enfermedades. Estos criterios de actuación se traducen, regularmente, en acción conjunta o complementaria en ambos niveles, central y regional. En caso de investigación de brotes, se actúa en colaboración con otras ramas del Departamento, como por ejemplo, el Programa de Inmunización, el Instituto de Laboratorios,

TABLA V

Enfermedades y Condiciones de Declaración Obligatoria en Puerto Rico

Amebiasis
Cólera
Conjuntivitis
Dengue
Difteria
Encefalitis
Escabiosis
Esquistosomiasis (bilharzia)
Fiebre amarilla
Fiebre recurrente transmitida por piojos
Fiebre reumática
Fiebres tifoidea y paratifoidea
Gastroenteritis
Gonorrea
Hepatitis A, B, y no especificada
Histoplasmosis
Impétigo
Influenza
Inmunodeficiencia adquirida, síndrome de ("AIDS")
Intoxicaciones alimentarias
Lepra
Leptospirosis
Malaria
Meningitis (aséptica, meningocócica, u otras)
Mononucleosis
Parotiditis
Peste (bubónica o neumónica)
Poliomielitis
Pulmonía
Rabia humana
Rubéola (sarampión alemán, "rubella")
Rubéola congénita, síndrome de
Salmonelosis
Sarampión común
Shigelosis
Sífilis
Tétanos
Tifo (exantemático y transmitido por piojos)
Tos ferina
Triquinosis
Tuberculosis
Varicelas
Viruelas
Cualquier enfermedad infecciosa no usual
Brote de cualquier enfermedad

y la Secretaría Auxiliar de Salud Ambiental. La División comparte con el gobierno federal, desde el 7 de octubre de 1983, la responsabilidad de controlar la entrada de infecciones traídas desde el extranjero. Desde esa fecha, en que cerró la estación de cuarentena del aeropuerto de Isla Verde, es la División de Epidemiología la que debe proveer asesoramiento médico en caso de que se identifique un pasajero afectado con síntomas que sugieran una enfermedad contagiosa.

H. "Para 1990 al menos 50% de las personas en poblaciones señaladas por el Comité consultor sobre prácticas de inmunización del "U.S. Public Health Service" deben estar inmunizadas con nuevas vacunas autorizadas para uso clínico rutinario, dentro de los cinco años después del licenciamiento de cada vacuna." (Este mismo objetivo también se asignó al área de inmunizaciones, y bajo ese tópico se discutirá en un artículo futuro.)

Mejoramiento en los servicios de vigilancia y evaluación

I. "Para 1990 los sistemas de notificación de datos en todos los Estados deben ser capaces de vigilar el comportamiento epidemiológico de agentes infecciosos comunes que no están ahora sometidos a la vigilancia sanitaria tradicional (por ejemplo, enfermedades respiratorias, enfermedades gastrointestinales, otitis media), y de medir el efecto de estos agentes en los costos de cuidado médico y en la productividad a nivel local y estatal, y, por extensión, a nivel nacional." — P

A diferencia de muchos estados de la Unión, Puerto Rico incluye varias condiciones comunes entre las enfermedades de declaración obligatoria, como por ejemplo, influenza y síndromes gripales, varicelas y gastroenteritis. Esta información se exige de forma englobada (números de casos por semana) y se genera usando criterios clínicos, sin confirmación de laboratorio virológico. Al presente no se están haciendo correlaciones de esta información con los datos sobre costos médicos o productividad laboral.

J. "Para 1990 la extensión de epidemias de enfermedades virales respiratorias y entéricas debe poder ser pronosticada antes de éstas cumplir dos semanas de su aparición, mediante sistemas de vigilancia que utilicen centinelas a través de la comunidad." — I

Este objetivo hace referencia a los sistemas de vigilancia que utilizan a médicos privados o salas de emergencias como informantes veloces de datos consistentes, aunque no necesariamente representativos de la comunidad en general. No hay, al momento, un sistema así en acción en Puerto Rico ni, por lo tanto, datos utilizables para predecir prontamente la extensión de epidemias virales. Los médicos e instituciones con interés en participar en este tipo de sistema pueden comunicarse con la División de Epidemiología (758-5344, 758-5422).

K. "Para 1990 todos los departamentos de salud estatales deben estar enlazados por computadora a agencias de salud federales para las actividades rutinarias de recolección, análisis y diseminación de datos de vigilancia epidemiológica, transmisión rápida de mensajes y

consultoría en la investigación de epidemias." — I

No hay, al presente, participación del Departamento de Salud en una red federal de comunicaciones por computadora para salud pública.

L. "Para 1990 los laboratorios a través de la nación deben estar enlazados para rastrear agentes infecciosos y patrones de resistencia a antibióticos, y para diseminar información." — P

Los laboratorios del Departamento de Salud participan, como los laboratorios de otros estados, en el sistema de información que mantienen los laboratorios de los Centers for Disease Control. El Instituto envía datos respecto a sus hallazgos y recibe información sobre lo que ocurre en otros laboratorios de los estados, pero los laboratorios clínicos privados o de hospitales individuales no participan en esta comunicación.

Conclusiones

Dos factores, operantes simultáneamente desde 1978, han influido para mejorar la vigilancia y control de las enfermedades infecciosas en Puerto Rico. El primer factor decisivo ha sido la identificación de una persona en cada región de Salud con la responsabilidad de estimular la notificación de casos de enfermedades de declaración obligatoria y la obligación de revisar los informes tan pronto llegan a sus manos, para tomar la acción necesaria. El segundo factor, la implantación de programas de control de infecciones nosocomiales, ha mejorado grandemente la vigilancia epidemiológica en los casos hospitalizados y ha influido también para conseguir un mejor diagnóstico y manejo de los casos. En esto también han influido los médicos especialistas en enfermedades infecciosas, que ahora son parte integrante de la facultad médica de muchos hospitales pero antes eran muy escasos.

De los once objetivos discutidos en este artículo, tres deben trabajarse empezando por una definición del problema (la incidencia de pulmonía neumocócica en Puerto Rico) o por la implementación de un sistema nuevo (centinelas epidemiológicos en la comunidad, comunicaciones por computadora con agencias federales de salud). El objetivo que más se acerca a la meta se refiere a la incidencia de meningitis bacteriana. Queda trabajo por hacer para asegurar que el objetivo se alcanza. Hay que refinar el sistema de vigilancia para asegurar que se reportan todos los casos y que se transmite correctamente la información pertinente. Además hay que evitar que la incidencia de la enfermedad aumente, de hoy a 1990. Para siete objetivos más (A, B, E, F, G, I, E) hay al momento un esfuerzo de recogida de datos y/o un programa establecido para conseguir el objetivo. Alcanzar la meta en 1990 exigirá el asignar prioridades, fondos y facilitación administrativa a las siguientes actividades: estudios epidemiológicos (prevalencia de portadores de HBsAg en Puerto Rico), identificación de contactos (tuberculosis), evaluación de sistemas (impacto de los programas de control de infecciones nosocomiales y factores que determinan su funcionamiento), capacitación de personal (para la investigación y control de enfermedades infecciosas), estudios económicos (efectos de las

epidemias de enfermedades comunes en la productividad laboral), y el desarrollo de sistemas de comunicación (para compartir información entre laboratorios).

Muchos estados y jurisdicciones menores (condados, ciudades, etc.) han utilizado estos objetivos para 1990 como regla para medir sus actividades en el campo de la prevención.^{17, 18} En un seminario llevado a cabo en los Centros de Control de Enfermedades ("Centers for Disease Control") de "U.S. Public Health Service" en septiembre de 1982 se discutieron los estudios que ha llevado a cabo cada estado o jurisdicción y las dificultades que prevén en la implantación de medidas eficaces para lograr los objetivos de salud para 1990. Se identificaron las siguientes categorías generales de necesidades en las agencias de salud en toda la nación: 1. investigación operacional y evaluación de estrategias de intervención; 2. ayuda técnica en el desarrollo de datos para uso en los programas; 3. interpretación y transferencia de la información; 4. programas de entrenamiento y desarrollo profesional; 5. formación de grupos de interés en salud pública con influencia a nivel local y estatal; 6. formación de estos grupos a nivel nacional; 7. diseminación de información al público.¹⁹ Las necesidades en Puerto Rico no son, en consecuencia, la excepción a la regla.

En artículos futuros se irán examinando los objetivos relacionados con otras áreas de salud, primero las áreas de inmunizaciones y enfermedades de transmisión sexual, y luego los problemas de salud que no son infecciosos.

Abstract: In 1980 the U.S. Public Health Service published its goals for the improvement of the health of the country's residents for the next ten years. Of the eleven national health goals for 1990 alluding to the surveillance and control of infectious diseases, eight are under study and/or being pursued locally, and three need to be developed from the very basic stages. The achievement of these objectives in Puerto Rico, as in other states, requires the cooperation of many governmental, academic and voluntary institutions. Future article will discuss the national goals that refer to other health areas.

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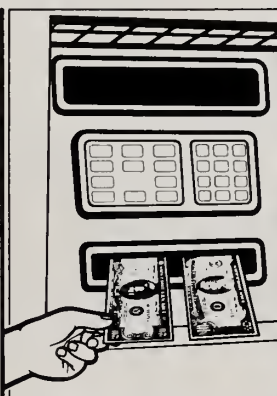
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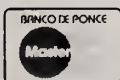
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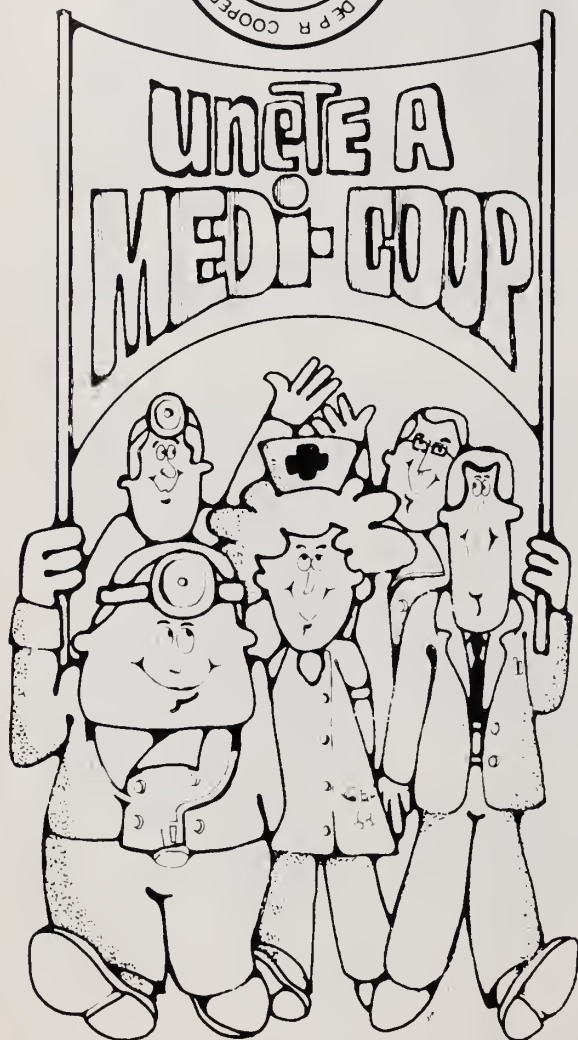


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BRIEF SUMMARY

PROCARDIA® (nifedipine) CAPSULES

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INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates. PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis. Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy. Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77° F (15° to 25° C) in the manufacturer's original container.

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- 2) Angina where the clinical presentation suggests a possible vasospastic component.
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Radionuclide Cystography in Pediatric Patients

José R. Vázquez, M.D.
Frieda Silva de Roldán, M.D.
William Ruiz, M.D.

The incidence of vesicoureteral reflux is 50% in children with urinary tract infection but only 8% in adults with bacteriuria.¹ Vesicoureteral reflux may cause permanent damage to the kidneys through one or both of two mechanisms: 1. pyelonephritis, and 2. hydronephrosis. With few exceptions, pyelonephritis - acute, chronic or healed - is secondary to vesicoureteral reflux.

The "gold standard" method to study vesicoureteral reflux has been roentgenographic cystography. Recently, there has been a growing interest in the use of radionuclide techniques for the detection of vesicoureteral reflux. The availability of gamma camera imaging and computer analysis, coupled with more ideal radiopharmaceuticals, have provided an effective method for evaluating not only the anatomic but also functional parameters of vesicoureteral reflux.

Case Summary

A nine months old male infant with previous history of urinary tract infections was admitted at the age of five months with a chief complaint of fever and seizures. Urine cultures revealed infection with *E. coli*. This prompted further urological evaluation in view of recurrence. A direct voiding cystography showed bilateral vesicoureteral reflux (grade IV) and hydronephrosis. Excretory urogram done on August 11, 1981 disclosed some fullness of the right pelvicalyceal system compatible with mild, chronic changes secondary to vesicoureteral reflux. On February 3, 1982 he was referred to us for a direct radionuclide cystography. A bilateral ureteral reimplantation was performed on February 23.

Method

No preparation or sedation is needed for a direct radionuclide cystogram.² The patient is placed supine on the scanning cart with the gamma camera underneath the table. Catheterization is performed using aseptic tech-

niques. The content of the bladder is emptied and the catheter is connected to a bottle of normal saline. After normal flow is established, 1 mCi of ^{99m}Tc-pertechnetate is introduced into the system and dynamic computer acquisition is started. Bladder filling should be monitored continuously. In most children, bladder capacity ranges from 50 to 200 ml. Normally, the radiotracer remains in the urinary bladder and there is no visualization of the ureters nor the kidneys as shown in Fig. 1. If reflux occurs (Fig. 2) the saline volume infused up to that point is noted. The total volume of instilled saline is recorded. The patient is then seated on a bedpan in front of the camera. The catheter is removed and the patient is encouraged to void. The dynamic sequence of voiding is recorded in the computer and on serial images. In infants, the voiding phase of the examination is done in the supine position. All the urine is collected and its volume is measured.

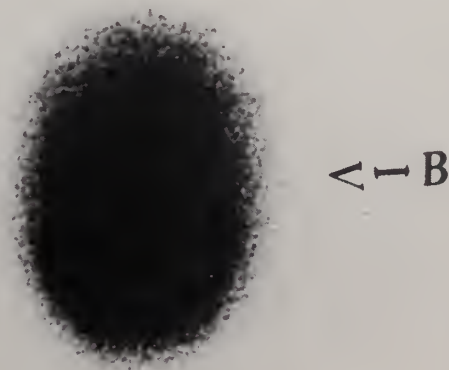


Fig. 1: Normal radionuclide cystogram. There is no visualization of the ureters nor the kidneys. B = bladder.

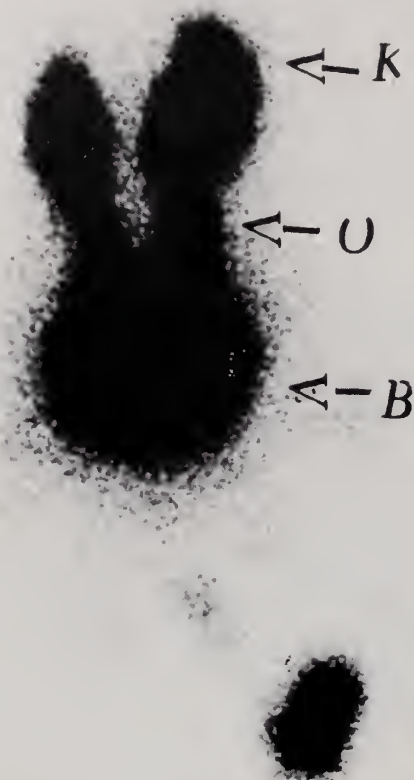


Fig. 2: Abnormal radionuclide cystogram showing severe bilateral ureterovesical reflux. K = kidney; U = ureter; B = bladder.

Discussion

The direct radionuclide cystogram has been shown to be a reliable and sensitive technique in the diagnosis and follow up of reflux. This study provides several advantages over conventional roentgenographic cystography. Conway et al have shown these advantages to be a greater sensitivity for detecting reflux, a marked decrease in radiation, and yield of quantitative data reflecting functional aspects of the bladder.^{3, 4} The quantitative determinations include: 1. the total bladder volume, 2. the bladder volume at which reflux occurs, 3. the volume of reflux into the upper tracts, and 4. the residual bladder volume after voiding.⁵

The major advantage of the radionuclide cystogram over the standard radiographic study, specially when dealing with pediatric patients, is radiation dose reduction. With the nuclear study, the calculated dose to the bladder wall during a 30 minutes examination time is 30 millirads and radiation to the gonads is less than 5 millirads. With the contrast roentgenographic technique, gonadal dose is several hundred times greater.⁶ The major disadvantage of the nuclear technique is its rather limited resolution which makes more difficult the detection of structural lesions.

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MEDICINA AL DIA

Therapeutic Progress: Trimethoprim-Sulfamethoxazole

R. Ruiz López, M.D.
S. Saavedra, Ph.D., M.D.
C.H. Ramírez-Ronda, M.D., F.A.C.P.

Abstract: Trimethoprim-Sulfamethoxazole (TMP-SMX) is a fixed-dose combination antibiotic also known as co-trimoxazole and available in oral and intravenous preparations. The oral preparation was introduced in 1968 and has been used in the U.S.A. since 1973 for a variety of infections, particularly urinary tract infections, and also for the treatment of acute otitis media in children. Recently the parenteral form of this combination became available for the treatment of some seriously ill patients who will benefit of the intravenous administration of the drug.

We present its chemistry, mechanism of action, pharmacology, antibacterial activity, dosage, toxicity and clinical use.

Trimethoprim-Sulfamethoxazole (TMP-SMX) is a fixed-dose combination antibiotic which exerts a synergistic effect on bacteria. In its oral preparation it has been widely used for the treatment of urinary tract infections and also for the treatment of bronchitis, shigellosis, *Pneumocystis carinii* pneumonia, acute otitis media in children and *Salmonella typhosa* resistant to both chloramphenicol and ampicillin. Recently the parenteral preparation of this drug has been available for the treatment of patients who will benefit from the intravenous administration of the medication probably because of serious infections with *Pneumocystis carinii* or because intolerance of oral medications due to severe vomiting.

Chemistry and Mechanism of Action

Biochemical structures of TMP & SMX are shown in Figure I. Trimethoprim is a diaminopyrimidine that competitively inhibits the activity of the enzyme dihydro-

folate reductase thus blocking the conversion of dihydrofolic acid to tetrahydrofolic acid which is needed in the synthesis of folinic acid. Sulfamethoxazole is a sulfonamide that competitively inhibits the utilization of p-aminobenzoic acid in the synthesis of folic acid. In this way, the combined preparation of TMP-SMX provides a synergistic bactericidal effect by blocking two consecutive steps in folinic acid metabolism needed in the biosynthesis of bacterial nucleic acids.¹

Figure I

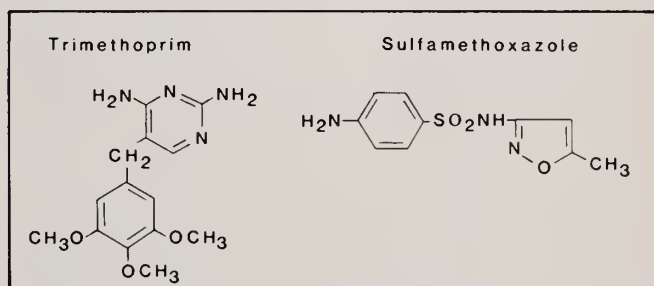
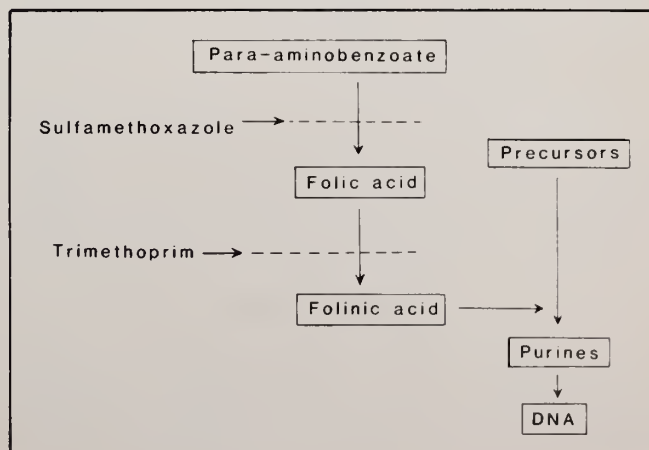


Figure II



Infectious Disease Program, and Departments of Medicine and Research, VA Medical Center and University of Puerto Rico School of Medicine, San Juan, Puerto Rico 00936.

Request reprints to: S. Saavedra, Ph. D., M.D., VA Medical Center, Infectious Disease Research (151), G.P.O. Box 4867, San Juan, Puerto Rico 00936.

Pharmacology

Even though other sulfonamides have been combined with trimethoprim and related drugs in the treatment of malaria, sulfamethoxazole was selected over the other short acting sulfonamides for the fixed-dosage combination because both agents are absorbed, distributed, metabolized and excreted in similar rate.^{2, 3}

When the oral preparation is used, peak blood levels for the individual components occurs 1-4 hours after administration. As it is expected, peak serum or plasma concentrations of TMP-SMX occurs more rapidly with the intravenous preparation having them in about 1 hour after intravenous infusion of a single dose. Because many patients have variable oral absorptions, peak concentrations are often higher and more predictable after intravenous administration. The half-lives of both compounds are relatively the same (10 hours) regardless of whether they are administered individually or combined, orally or intravenously.³⁻⁵

Pharmacokinetic studies with intravenous trimethoprim suggest an age dependent half-life of this drug with mean half life in a range from 5.5 hours in children of 1-10 y/o to 12.8 hours in patients older than 20 y/o.⁶

The optimal ratio of serum concentrations of TMP & SMX for the maximal synergistic effect against most susceptible bacteria is 1:20 respectively and this is the steady-state ratio achieved in blood after repeated administration of the drug orally or intravenously.¹

Once the TMP-SMX is in the blood, it is bound to plasma proteins about 66% for SMX and 45% for TMP.³ In addition to the protein bound forms of both compounds, the SMX also exists in blood as free and conjugated forms and the TMP as free and metabolized forms. Tissue concentrations of sulfamethoxazole are generally less than concurrent serum or plasma concentrations. TMP often penetrates extravascular tissues, especially fatty tissues, to a greater extent than does sulfamethoxazole. Concentrations of TMP in saliva, human breast milk, noninflamed prostatic tissue, seminal fluid, inflamed lung tissue and bile often exceed those in serum. Specifically, TMP concentration in prostatic fluid are generally at least three times the serum concentrations.⁷⁻⁹ Both TMP and SMX cross the human placenta. Little information is available about concentrations of either antibiotic in brain tissue and cerebrospinal fluid with uninflamed meninges in humans.¹⁰

About 10-30% of TMP is metabolized and 20% of SMX is acetylated or conjugated. These metabolites are bacteriologically inactive.¹

Excretion of both compounds regardless of whether they are intact or metabolized occurs chiefly by the kidneys through both glomerular filtration and tubular secretion. Due to this the intact compounds are also excreted in the bile. Urine concentrations of both TMP and SMX are considerably higher than are in the blood.¹¹

Antibacterial Activity

In vitro the spectrum of antibacterial activity of TMP-SMX includes a variety of gram-positive and gram-negative microorganisms. Gram-negative bacilli as *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*,

indole-positive *Proteus* species, *Haemophilus influenzae*, *Shigella flexneri* and *Shigella sonnei* are usually susceptible. In the gram-positive group, *Streptococcus pneumoniae* is highly susceptible to these compounds. Other microorganisms usually susceptible includes *Brucella* species, *Chlamydia trachomatis*, *H. ducreyi*, *M. kansasii*, *M. marinum*, *Nocardia asteroides*, *Pneumocystis carinii*, *Pseudomonas cepacia*, *P. pseudomallei* and *Salmonella typhi*. TMP-SMX has virtually no activity against *Pseudomonas aeruginosa* and anaerobes.¹²⁻¹⁶

In vitro studies have shown that bacterial resistance develops more slowly with the combined form than with the TMP or SMX individually.¹⁷

Toxicity

Adverse reactions reported are essentially the same with oral and parenteral TMP-SMX. The most frequently reported are: nausea, vomiting, skin rash and thrombocytopenia, all in less than one-twentieth of patients. Local reaction, pain and slight irritation in the intravenous site of administration had been reported but are infrequent; thrombophlebitis is rare.¹⁸

Severe adverse effects are rare, but there are reported reactions including hematological reactions as hemolysis in patients with G-6-P dehydrogenase deficiency, megaloblastic anemia, aplastic anemia and granulocytopenia. Serious skin reactions including Stevens-Johnson Syndrome have been reported.¹⁸

Precautions should be taken in patients receiving warfarin since both oral and parenteral forms may prolong prothrombin time in these patients.¹⁹

The preparation should be given cautiously in patients with impaired renal or hepatic functions, folate deficiency and blood dyscrasias.¹⁹

The TMP-SMX should not be used in pregnant or nursing women because it passes the placenta and is excreted in the milk causing potential risk to the fetus.¹⁹

Clinical Use

Genitourinary Infections:

TMP-SMX is indicated for the treatment of chronic and recurrent urinary tract infections caused by susceptible bacteria.^{1, 20} The intravenous preparation can probably be used in patients with severe urinary tract infections who are too ill to take the oral medication and the oral preparation can be substituted whenever the patient's condition permits. However, it is our opinion that if the patient is too ill he will probably benefit of a broader spectrum antibiotic treatment as an aminoglycoside.

Cultures and susceptibility tests should always be done to determine the susceptibility of the organism to the antibiotic. It must be remembered that the usefulness of any antibacterial agent is limited by the increasing frequency of resistant organisms and this is particularly true in the case of urinary tract infections.¹⁷

Also TMP-SMX had been used for prophylaxis against recurrent urinary tract infections.²¹⁻²⁴

TMP-SMX is highly effective in acute bacterial prostatitis when susceptible organisms are demonstrated.

When no pathogen is isolated and particularly in men older than 35 years of age (when *Chlamydia* is an unusual pathogen), a trial of TMP-SMX is reasonable. TMP-SMX may also be useful in epididymitis and orchitis.^{25, 26}

TMP-SMX is an effective alternative therapy for uncomplicated gonococcal urogenital and pharyngeal infections and may be particularly useful with penicillinase-producing strains of gonococci. TMP-SMX is ineffective against syphilis, however, it seems promising for treatment of lymphogranuloma venereum and chancroid (*H. ducreyi*) infections. The *in vitro* sensitivity of TMP-SMX against *C. trachomatis* is encouraging, but more clinical trials assessing *in vivo* effectiveness are needed. Most of the activity against *C. trachomatis* seems to be due to SMX alone.^{14, 27, 28}

Gastrointestinal Infections:

Because of increasing numbers of ampicillin-resistant *Shigella* strains, TMP-SMX may be considered the antibiotic of choice for infections caused by these organisms. Even though there are reports that demonstrated *Shigella* strains resistant to TMP-SMX.²⁹

TMP-SMX may be useful in treating enteric fever caused by *S. typhi* and *S. paratyphi*, especially when chloramphenicol-resistant strains are isolated.²⁹

TMP-SMX may be effective as prophylaxis against and treatment of traveler's diarrhea.³⁰

Respiratory Tract Infections:

The activity of TMP-SMX against *S. pneumoniae* and *H. influenza* accounts for its usefulness in acute otitis media and acute bronchitis.^{31, 32}

TMP-SMX may be as effective as ampicillin for treatment of acute bronchitis and as effective as doxycycline for prophylaxis against bacterial pulmonary infections in patients with chronic bronchitis and cystic fibrosis. TMP-SMX may also be useful in sinusitis and pneumonitis when susceptible pathogens have been identified.³³

Pneumocystis carinii pneumonia is a life-threatening infection in immunosuppressed patients for which TMP-SMX is the antimicrobial agent of choice. The response to intravenous TMP-SMX in these cases equalled or exceeded the previously reported with the oral preparation.^{34, 35}

Another infections where TMP-SMX had been useful are the ones with *Nocardia asteroides*, but there could be resistance.^{36, 37}

Other Infections:

Intravenous TMP-SMX may also be useful to treat other enteric gram-negative bacteria infections outside of the urinary tract, particularly when they are resistant to other antimicrobial agents such as the aminoglycosides, but there is only few data available in this respect. Also the intravenous drug will probably be useful in treating serious systemic infections with *Haemophilus influenzae* resistant to both ampicillin and chloramphenicol but there is also few data available.³⁸

There are also isolated cases reported in which TMP-SMX had been successfully used in treating several other

conditions.³⁸ One case of *Klebsiella pneumoniae* meningitis where TMP-SMX given intravenously achieved bactericidal levels in CSF and clinical resolution of the meningitis.³⁹ In another case, a man with stenosis of the aortic valve acquired endocarditis after abdominal surgery. *Klebsiella pneumoniae* and *Acinetobacter calcoaceticus* were cultured from his blood. The blood cultures remained positive despite intravenous gentamicin and cephalothin to which the organisms were sensitive *in vitro*. Ultimately, the blood was sterilized by a combination of gentamicin and trimethoprim-sulfamethoxazole taken orally. The course of the patient was complicated by cardiac arrest and pericardial tamponade caused by a valve ring abscess and a dissecting mycotic aneurysm of the coronary sinus of Valsalva. Aortic valve replacement and right coronary artery bypass were performed. A prolonged course of TMP-SMX was given postoperatively, and the patient has had no evidence of recurrent infection after five years. TMP-SMX, in combination with other antibiotics has been successfully used to treat other patients with bacterial endocarditis and thus may be an alternative for patients in whom conventional therapy has failed.⁴⁰

In vitro susceptibility data demonstrate inhibition of some mycobacteria by TMP-SMX. *M. kansasii*, *M. marinum* and *M. scrofulaceum* are moderately sensitive, whereas *M. tuberculosis* and *M. chelonae* are generally resistant. Other mycobacteria show variable susceptibility.⁴¹

Dosage

Dosage for TMP-SMX depends on infection and administration routes. Recommendations for adults are summarized in Table I, including the length of treatment for each condition.

When oral preparation is preferred, two different preparations are available. The single-strength (SS) consists of 80 mg of TMP and 400 mg of SMX and the double-strength (DS) one consists of 160 mg of TMP and 800 mg SMX.

For severe and serious infections the intravenous administration is preferred. The intravenous preparation contains 80 mg of TMP and 400 mg of SMX in each 5 ml ampule. The recommended dosage is based on the TMP component. When renal insufficiency is present, the dosage of the combined antibiotic should be adjusted if creatinine clearance is less than 30 ml/min. Patients with creatinine clearance of 15-30 ml/min should receive half the usual daily dosage (keeping the frequency of administration constant). If creatinine clearance is below 15 ml/min the drug should not be used.^{2, 5, 42}

Many women with lower urinary tract symptoms suggestive of cystitis can be cured with one double-strength tablet. Otherwise, conventional therapy for woman or man with cystitis is one single-strength tablet every 6 or 8 hours or one double-strength tablet every 12 hours for 10 days.⁴³⁻⁴⁵ When treatment of asymptomatic bacteriuria is indicated, an initial trial with the same regimen as is used for conventional treatment of cystitis is acceptable.⁴⁶ For prophylaxis against recurrent U.T.I. one single strength tablet daily is advised.²⁴

TABLE I

Infection	DOSAGE*				
	ORAL		INTRAVENOUS		
	Tablets**	Frequency	Trimethoprim equivalent (mg/kg per day)	Frequency	Duration***
<u>Respiratory tract</u>					
<u>Otitis media</u>					
Adults	1 SS	Every 6 hours			7-10 days
Children	8-10 mg/kg/d (liquid)	Every 8-12 hours			7-10 days
Acute bronchitis	1 SS	Every 6 hours			7-10 days
Prophylaxis against acute infectious exacerbations in chronic bronchitis	1 SS	Daily			7 days each month or alternate weeks
<u>Pneumocystis carinii pneumonia</u>	2 DS	Every 6 hours	20	Every 6 hours	14 days
<u>Nocardia asteroides</u> infections	3 SS or 1 DS	Every 6 hours	10-15	Every 6 hours	6 months to 1 year
<u>Genitourinary tract</u>					
<u>Upper urinary tract</u>					
Pyelonephritis	1 DS	Every 6 or 8 hours	8-10	Every 6 hours	10-14 days
<u>Lower urinary tract</u>					
Cystitis	1 DS	Once			
Single dose, female	1 SS	Every 6 or 8 hours			7-10 days
Conventional, female or male	or 1 DS	Every 12 hours			7-10 days
	1/2 SS	Every day			Variable
Urinary tract prophylaxis	or 1 SS	Every other day			Variable
Asymptomatic bacteriuria (when treatment is indicated)	1 SS	Every 6 or 8 hours			7-10 days
<u>Prostatitis</u>	1 DS	Every 6 hours	10	Every 6 hours	7-10 days
Acute	Then 1 SS	Every 6 hours			14-35 days
	1 SS	Every 8 or 12 hours			Up to 12 weeks
Chronic	or 1 DS	Every 12 hours			Up to 12 weeks
<u>Gastrointestinal tract</u>					
<u>Shigella</u>	1 DS	Every 6 hours	8-10	Every 6 hours	5-7 days
<u>Salmonella enteric fever</u>	1 DS	Every 6 hours	8-10	Every 6 hours	10-14 days
<u>Enteropathogenic E. coli</u>					
Adults	1 SS	Every 6 hours	5-7	Every 6 hours	5-7 days
Children	5-7 mg/kg/d (liquid)	Every 6 hours			
Traveler's diarrhea prophylaxis	1 DS	Every 12 hours			Duration of exposure
<u>Veneral disease</u>					
<u>Neisseria gonorrhoea</u>	4 DS	Once			
(urethritis, cervicitis)	or 2 DS	Every 12 hours			5 days
<u>Lymphogranuloma venereum</u>	1 DS	Every 12 hours			7-10 days
	or 3 SS				
<u>Chancroid (Haemophilus ducreyi)</u>	1 DS	Every 12 hours			10 days

*Adult dosage unless otherwise specified.

**DS = double strength; SS = single strength.

***Entire length of the treatment regimen, whether the initial treatment is intravenous and the subsequent treatment is oral or the entire treatment regimen is oral or intravenous therapy alone.

Resumen: Trimethoprim-Sulfamethoxazole (TMP-SMX), también conocida como co-trimoxazole, es una combinación de antibióticos disponible en dosis constante en forma oral y parenteral. La preparación oral se introdujo en 1968 y ha sido utilizada en los Estados Unidos de América desde 1973 para el tratamiento de un número variado de infecciones, especialmente para infecciones del tracto urinario y otitis media aguda en niños. Recientemente la forma parenteral ha sido introducida y está disponible para el tratamiento de algunos pacientes seriamente enfermos que se benefician de la administración endovenosa de la droga.

Acknowledgement

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Nuestro Pasado Médico Histórico



José Elías y Herreros (1847-1908)

José G. Rigau Pérez, M.D., F.A.A.P.

Los informes del doctor José Elías y Herreros sobre la vacunación contra viruela son la única documentación que tenemos de la labor técnica de los servicios de salud pública en Puerto Rico en los últimos años de la colonia española.¹⁻³ La foto que aquí reproducimos fue publicada en 1900.⁴



Elías nació el 22 de marzo de 1847 en Soto de Carreros, provincia de Logroño. Graduado de médico-cirujano, ingresó al Cuerpo de Sanidad Militar el 9 de abril de 1872. Fue vicedirector del Instituto Provincial de Vacuna de Puerto Rico desde la fundación del mismo, el 2 de agosto de 1882, hasta 1884, en que asumió el cargo de director. Ocupó esta posición hasta 1887 y luego de 1891 hasta al menos 1897. Fue socio correspondiente de la Sociedad Jenneriana Matritense, y sus trabajos sobre la vacunación contra viruela merecieron una medalla de oro en la exposición celebrada en San Juan con motivo del cuarto centenario del descubrimiento de Puerto Rico. Después de la repatriación de las tropas españolas en 1898 fue condecorado con la Orden del Mérito Militar. Falleció en Santurce, provincia de Vizcaya, el 12 de agosto de 1908, de una afección cardíaca.⁵

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ARTICULOS ESPECIALES

Liver Transplantation: Consensus Conference

Since performance of the first human orthotopic liver transplantation in 1963, more than 540 such operations have been performed in four medical centers in the United States and western Europe. Additional liver transplantation procedures have been performed in other parts of the world and, more recently, in several other American medical centers. Although extremely demanding and expensive, the operation has been shown to be technically feasible, and interpretable results have been reported from all four primary transplant centers.

These clearly demonstrate that liver transplantation offers an alternative therapeutic approach that may prolong life in some patients suffering from severe liver disease that has progressed beyond the reach of currently available treatment and consequently carries a predictably poor prognosis. However, substantial questions remain regarding selection of patients who may benefit from liver transplantation; the stage of their liver disease at which transplantation should be performed; survival and clinical condition of patients beyond the initial year after transplantation; and overall long-range benefits and risks of transplantation in the management of specific liver diseases.

To resolve some of these questions, the National Institutes of Health on June 20 through 23, 1983, convened a Consensus Development Conference on Liver Transplantation. After two days of expert presentation of the available data, a Consensus Panel consisting of hepatologists, surgeons, internists, pediatricians, immunologists, biostatisticians, ethicists, and public representatives considered the offered evidence to arrive at answers to the following key questions:

1. Are there groups of patients for whom transplantation of the liver should be considered appropriate therapy?
2. What is the outcome (current survival rates and complications) in different groups?

3. In a potential candidate for transplantation, what are the principles guiding selection of the appropriate time for surgery?

4. What are the skills, resources, and institutional support needed for liver transplantation?

5. What are the directions for future research?

1. Are There Groups of Patients for Whom Transplantation of the Liver Should Be Considered Appropriate Therapy?— Liver transplantation is a promising alternative to current therapy in the management of the late phase of several forms of serious liver diseases. Candidates include children and adults suffering from irreversible liver injury who have exhausted alternative medical and surgical treatments and are approaching the terminal phase of their illness. In many forms of liver disease, the precise indications and timing of liver transplantation remain uncertain or controversial.

Prolongation of life of good quality for patients who would otherwise have died has been reported in the following conditions:

- *Extrahepatic biliary atresia* is the most common cause of bile duct obstruction in the young infant. Patients who fail to respond to hepatoportoenterostomy (Kasai procedure) often benefit from liver transplantation. Recent data suggest that as many as two thirds of these patients survive for one year or more after transplantation.

- *Chronic active hepatitis* is caused by viral infections or drug reactions, but many cases remain unexplained. Some patients with progressive liver failure are candidates for transplantation. Currently, exceptions seem to include drug-induced chronic active hepatitis, which usually responds to removal of the chemical agent, and hepatitis B-induced disease in which viremia persists. In the latter instance, rapid reappearance of infection with progressive liver failure has been reported after transplantation.

- *Primary biliary cirrhosis* is a slowly progressive cholestatic liver disease. Results of transplantation appear favorable for patients with end-stage liver injury. The procedure may improve the quality of life.

- *Inborn errors by metabolism* may cause end-stage liver damage or irreversible extrahepatic complications. Transplantation may be appropriate for such patients.

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● *Hepatic vein thrombosis* (Budd-Chiari syndrome) often results in progressive liver failure, ascites, and death. Patients who have not responded to anticoagulation or appropriate surgery for portal decompression may be candidates for transplantation.

● *Sclerosing cholangitis*, a chronic nonsuppurative inflammatory process of the bile ducts, may cause liver failure. Less favorable results after transplantation in this group may be caused by prior multiple surgical procedures, a diseased extrahepatic bile duct, the presence of biliary infection, or other factors.

● *Primary hepatic malignant neoplasms* confined to the liver but not amenable to resection may be an indication for transplantation. Results to date indicate a strong likelihood of recurrence of the malignant neoplasm. Nevertheless, the procedure may achieve substantial palliation.

● *Alcohol-related liver cirrhosis and alcoholic hepatitis* are the most common forms of fatal liver disease in America. Patients who are judged likely to abstain from alcohol and who have established clinical indicators of fatal outcome may be candidates for transplantation. Only a small proportion of alcoholic patients with liver disease would be expected to meet these rigorous criteria.

Although *fulminant hepatic failure* with massive hepatocellular necrosis induced by hepatitis viruses, hepatotoxins, or certain drugs may warrant liver transplantation, rapid progression of the disease and multiorgan system failure frequently preclude this option.

2. What Is the Outcome (Current Survival Rates and Complications) in Different Groups?—The survival and complication rates of patients who have undergone liver transplantation are the major criteria for judging efficacy. Data are available from four locations (Pittsburgh; Cambridge, England; Hannover, West Germany; and Groningen, the Netherlands). The interpretation of the existing data on survival is extremely difficult because no control data are given for comparison, surgical techniques and drug therapies varied over time, and patient selection criteria and management differed across centers.

While sufficient data for thorough assessment of liver transplantation are not available to date, today certain trends appear to emerge:

● Patients currently being accepted for transplantation have a high probability of imminent death and a low quality of life in the absence of transplantation.

● Patients undergoing transplantation have an operative mortality (within one month) of 20% to 40%.

● One-year survival among transplant recipients since 1980 is favorable when compared with their expected course in the absence of transplantation.

● Since 1980, one-year survival appears improved over the earlier transplant experience.

● Individual patients have survived for many years with good quality of life after transplantation.

● Data are insufficient to evaluate survival rates beyond one year after transplantation with current technologies.

● Short-term quality of life is probably enhanced in many transplant survivors. We lack systematically gathered

information on quality of life among long-term survivors.

Severe nonlethal complications of transplantation frequently occur and must be taken into account in judging efficacy of this procedure. Massive hemorrhage is the most serious intraoperative and early postoperative problem. Other postoperative complications include renal dysfunction, rejection, biliary tract complications, graft vascular obstruction, and infection. With accumulating expertise in medical and surgical management and with new developments in technology (eg, intraoperative venovenous bypass and cyclosporine), these complications can be expected to diminish.

3. In a Potential Candidate for Transplantation, What Are the Principles Guiding Selection of the Appropriate Time for Surgery?—Selecting an appropriate stage for a given illness for liver transplantation is a complex issue: transplantation just before death may substantially diminish the lifesaving potential of the procedure, since hepatic decompensation in its latest stages poses a formidable surgical risk. Transplantation early in the course of hepatic decompensation may deprive a patient of an additional period of useful life.

An ideally timed liver transplantation procedure would be in a late enough phase of disease to offer the patient all opportunity for spontaneous stabilization or recovery, but in an early enough phase to give the surgical procedure a fair chance of success. For most patients, these phases are difficult to define prospectively. While no single best time for surgery can be specified, transplantation should be reserved for patients in any of the following phases of disease:

- When death is imminent.
- When irreversible damage to the CNS is inevitable.
- When quality of life has deteriorated to unacceptable levels.

The exact choice of the time for liver transplantation in a person requires the judgment of a qualified medical team and a well-informed patient. The following are offered as guidelines for individual liver diseases.

Extrahepatic Biliary Atresia

Biliary enteric anastomosis (hepatoportoenterostomy of Kasai) performed in the first two months of life provides substantial improvement for at least five years in one third of the patients, although cirrhosis and disappearance of the intrahepatic bile ducts occur with increasing age. While success of this procedure cannot be predicted for the individual patient it should be used as initial therapy for extrahepatic biliary atresia. In the absence of severe hepatic decompensation in these children, liver transplantation should be delayed as long as possible to permit the child to achieve maximum growth. In children with successful hepatoportoenterostomy, liver transplantation should be deferred until progressive cholestasis, hepatocellular decompensation, or severe portal hypertension supervene.

Multiple attempts at hepatoportoenterostomy or surgical portosystemic shunting render eventual transplant surgery technically more difficult and operationally

more dangerous and, therefore, should be avoided in favor of liver transplantation.

Chronic Active Hepatitis

The potential for spontaneous remission and the complex course of chronic active hepatitis make valid predictions of the subsequent course difficult except in the latest stages of the disease. Using strict criteria, patients can be recognized who have almost no chance of survival beyond six months. Such patients may be suitable candidates for transplantation.

Primary Biliary Cirrhosis

The indolent course of primary biliary cirrhosis and the potential for spontaneous improvement even in patients with advanced disease make transplantation potentially suitable only in the final stages of liver failure or when the quality of life has deteriorated to an unacceptable level.

Alpha₁-Antitrypsin Deficiency

Of the some 20 phenotypes in this genetic disorder, only Pi ZZ is associated with substantial hepatic disease in children. Of infants with this phenotype, neonatal cholestasis occurs in 5.5%. Jaundice usually is transient, clearing before 6 months of age, although biochemical evidence of activity may persist. Liver transplantation is indicated in children with Pi ZZ phenotype only when cirrhosis has developed and when evidence of hepatic failure is present.

Adults with alpha₁-antitrypsin deficiency may have liver disease associated with phenotype Pi ZZ, MZ, or SZ. If hepatic failure occurs, liver transplantation may be indicated.

Wilson's Disease

Patients with Wilson's disease usually are responsive to chelation therapy with penicillamine. However, some patients are initially seen with fulminant hepatic failure and/or progressive disease unresponsive to adequate chelation therapy. Liver transplantation may be indicated in these instances.

Crigler-Najjar Syndrome

Of the two types of this genetic disorder associated with severe unconjugated hyperbilirubinemia, patients with type I invariably experience bilirubin encephalopathy usually before 15 months of age. Because of the inevitability of CNS damage and the limitations of phototherapy, liver transplantation is indicated in such patients at an early age.

Miscellaneous Metabolic Diseases

A number of rare genetic diseases may involve the liver and cause cirrhosis and eventual hepatic failure.

Patients with tyrosinemia, Byler's disease, Wolman's disease, and glycogen storage diseases types 0 and IV may be candidates for hepatic transplantation.

Liver transplantation may also be indicated for patients with certain genetic diseases associated with

severe neurological complications, such as hereditary deficiency of urea cycle enzymes and disorders of lactate-pyruvate or amino acid metabolism.

Hepatic Vein Thrombosis

The course of hepatic vein thrombosis is variable, and, therefore, transplantation should be reserved for patients with severe hepatic decompensation. The possibility of later transplant surgery should not discourage the use of portal venous decompression when otherwise indicated.

Primary Sclerosing Cholangitis

No clinical, biochemical, serological, or histological factors have proved to be of value in predicting outcome. When appropriate attempts at biliary tract diversion and dilatation have failed, and death from liver failure is imminent, liver transplantation should be considered.

Alcoholic Liver Disease

At least 50% of the cases of cirrhosis in the United States are attributable to the abuse of alcohol, and alcohol abuse is the leading cause of hepatic morbidity and mortality.

Alcohol liver disease is most favorably affected by abstinence. The natural history of untreated alcoholic hepatitis and/or cirrhosis is extremely variable, and there are few precise prognostic indicators in any but the terminal phase of the disease.

Liver transplantation may be considered for the patients in whom evidence of progressive liver failure develops despite medical treatment and abstinence from alcohol.

4. What Are the Skills, Resources, and Institutional Support Needed for Liver Transplantation?—The requirements for conducting a liver transplantation program by a sponsoring institution are formidable. Accordingly, any institution embarking on this program must make a major commitment to its support. In addition to the full array of services required of a tertiary care facility and a program in graduate medical education, an active organ transplantation program should exist. Few hospitals are likely to meet these prerequisites.

Liver transplant recipients are seriously ill before surgery. The transplant effort is prodigious, and the post-operative intensive care interval, averaging two weeks, is punctuated by complications and frequent need for reoperation.

In this context, experts in hepatology, pediatrics, infectious disease, nephrology with dialysis capability, pulmonary medicine with respiratory therapy support, pathology, immunology, and anesthesiology are needed to complement a qualified transplantation team. Extensive blood bank support to provide the needed copious quantities of blood components is mandatory. Similarly, sophisticated microbiology, clinical chemistry, and radiology assistance are required. Emotional support for patient and family warrants psychiatric participation. Availability of effective social services to assist patients and families is indispensable.

The transplantation surgeon must be trained specifically for liver grafting and must assemble and train a

team to function whenever a donor organ is available. Institutional commitment to the program mandates that operating room, recovery room, laboratory, and blood bank support exist at all times. Allocation of intensive care and general surgical beds is important. Recruitment of a cohort of specialized nurses and technicians to staff these areas is necessary. Access to tissue-typing capability; ongoing research programs in liver disease, organ preservation, and transplantation immunology; and available hemoperfusion and microsurgical techniques are desirable attributes of a transplantation effort.

Participation in a donor procurement program and network is essential, and an interdisciplinary deliberative body should exist to determine on an equitable basis the suitability of candidates for transplantation.

Institutions conducting liver transplantation are obligated to prospectively collect and share data in a coordinated, systematic, and comprehensive manner in all patients selected as transplantation candidates, so that the role of liver transplantation in the treatment of patients with liver disease can be assessed properly. Additional information permitting cost-benefit analysis should be secured.

Finally, the panel believes that adherence to these guidelines detailing the essentials to conduct a transplantation program offers the best assurance of high quality in performing this very difficult operation.

5. What Are the Directions for Future Research?—The Consensus Panel identified several broad areas related to liver transplantation in which critically important information is either unavailable or so incomplete as to defy meaningful interpretation. It is recommended that a registry or clearinghouse be established for collection and evaluation of all available data on liver transplantation. Such a center would develop unified criteria for selection of patients for transplantation and for reporting and evaluating all data related to the outcome of the operation and the patient's postoperative and long-term condition. As methods of immunosuppression improve and the logistic obstacles are resolved, the feasibility and desirability of randomized clinical trials of liver transplantation should be explored for suitable subgroups of patients with specific liver diseases.

High priority also should be given to research projects related to several aspects of the transplant procedure itself. Means should be developed to improve preservation of human liver *ex vivo*, and criteria should be established to evaluate its viability. Improved control of organ rejection requires urgent attention; this includes thorough evaluation of the benefits and risks of cyclosporine as an immunosuppressive agent in liver transplantation. The design of the hemodynamic support system during transplantation needs evaluation and potential improvement. Research should be encouraged for developing better supportive measures for patients with liver failure, including maintenance of proper renal and cerebral function.

In the broad areas of the cause, pathogenesis, and natural course of chronic liver disease, present knowledge is fragmentary and incomplete, and research in these areas should be fostered and supported by all

available means. Particular attempts should be made to determine the possible role of liver transplantation in the management of hepatocellular carcinoma at a stage when metastatic spread appears remote. Similarly, approaches should be sought to limit infection of the transplanted liver by hepatotropic viruses. Finally, liver transplantation should be explored as a modality of replacement therapy in genetically determined multiorgan enzyme deficiencies.

Conclusion

After extensive review and consideration of all available data, this panel concludes that liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application. However, for liver transplantation to gain its full therapeutic potential, the indications for and results of the procedure must be the object of comprehensive, coordinated, and ongoing evaluation in the years ahead. This can best be achieved by expansion of this technology to a limited number of centers where performance of liver transplantation can be carried out under optimal conditions.

Members of the Consensus Development Panel were the following: Rudi Schmid, MD (panel chairman), San Francisco; Donald M. Berwick, MD, Boston; Burton Combes, MD, Dallas; Ralph B. D'Agostino, PhD, Boston; Stuart H. Danovitch, MD, Washington, DC; Harold J. Fallon, MD, Richmond, Va; Olga Jonasson, MD, Chicago; Charles E. Millard, MD, Bristol, RI; Linda Miller, MS, Washington, DC; Frank G. Moody, MD, Houston; William K. Schubert, MD, Cincinnati; Laurence Shandler, MD, Santa Fe, NM; Henry J. Winn, PhD, Boston.

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La Intervención del Terapeuta Ocupacional en el Equipo Interdisciplinario en el Área de la Salud Mental

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Resumen: En Puerto Rico se estima el problema de la salud mental como uno de los principales problemas de salud hoy día. Ante esta realidad se hace cada día más palpable la contribución de los diferentes profesionales de la salud en el manejo del paciente mental. El artículo ilustra los orígenes de la profesión de Terapia Ocupacional, se describen brevemente los diferentes marcos teóricos que sustentan el proceso de intervención de esta profesión en salud mental; así como la importancia del trabajo en equipo interdisciplinario. Se enfatiza la actividad con propósito como medio de tratamiento y se pone de manifiesto su relevancia para una buena labor en conjunto.

La necesidad de que el terapeuta ocupacional intervenga con el paciente en el área de la salud mental no es algo nuevo ni de reciente creación. Por tal motivo es imperativo señalar esquemáticamente algunos puntos sobre la valiosa aportación del terapeuta ocupacional, indicarle además sobre nuestra historia, definición, bases históricas, hacia qué y dónde enfocan nuestros servicios.

Desde el 1905 los terapeutas ocupacionales están interviniendo en el tratamiento de los pacientes mentales; esta profesión surgió como una necesidad para brindar un plan de tratamiento abarcador y de calidad a los pacientes.

Es curioso que muy pocos psiquiatras y otros profesionales relacionados con la salud tengan conocimiento de que nuestra profesión se fundó gracias al impulso de las ideas del Psiquiatra y Profesor, Adolf Meyer, quien para la época de 1892 señaló: "El uso del tiempo en actividades gratificantes y restaurativas es un "issue" fundamental en el tratamiento de los pacientes neuropsiquiátricos".¹ Además indicó que la enfermedad mental es un problema de vivir equilibradamente entre trabajo, juego, descanso y sueño. Por consiguiente, falta de equilibrio en estos factores trae enfermedad mental. Por estas ideas y por percatarse de que los pacientes necesitan la ayuda de ciertos profesionales que proveyeran actividades con propósito, que mantuvieran al individuo en equilibrio en

las tareas de su vida diaria; se considera al psiquiatra, Adolf Meyer, uno de los fundadores de nuestra profesión y uno de los exponentes máximos de nuestra filosofía de tratamiento. Esto queda muy ejemplificado en sus artículos "The Philosophy of Occupation" y "Legacy of Moral Treatment".

Nuestra profesión no solo surgió gracias al impulso del neuropsiquiatra, Adolf Meyer. Sino para 1905 la enfermera Susan Tracy,² quien se le considera históricamente como la primera terapeuta ocupacional, observó que el mantener a los pacientes ocupados, los libraba de tensiones nerviosas y se producía un sinnúmero de cambios positivos en los pacientes. Estas observaciones la inquietaron y la motivaron para que en 1906 desarrollara el primer curso para preparar profesionales que enseñaran actividades con propósito.

En aquel entonces una actividad con propósito estaba dirigida a cumplir unas metas terapéuticas después de una adecuada selección de las mismas. Se pensó en este tiempo que los artesanos serían los mejores maestros para brindar las actividades manuales. Pero dado el poco conocimiento de los artesanos sobre las condiciones físicas y emocionales de los pacientes; se determinó que las personas más aptas para brindar dichas actividades deberían de ser los profesionales con conocimientos en el campo de la salud, debidamente adiestrados en las actividades manuales, las cuales se utilizarían con fines de tratamiento.

Más adelante específicamente en 1915, Eleanor Clark Slage, Trabajadora Social, organizó la primera escuela de terapia ocupacional, basada en la filosofía del Dr. Adolf Meyer.

Es evidente que nuestra profesión desde sus comienzos tiene sus bases gracias a las aportaciones de psiquiatras, enfermeras y trabajadores sociales, profesionales de la salud, quienes se percataron de la necesidad de una profesión que reuniera los elementos necesarios para una intervención completa con el paciente. De esta forma se podría lograr una intervención adecuada, dirigida a que el paciente mantuviera una armonía dentro del contexto de su quehacer diario. Esto permitiría mejorar el estilo de vida de los pacientes; así como la calidad de vida.

En la actualidad nuestra profesión aún cuando se encuentra enriquecida con las nuevas tendencias teóricas, la tecnología avanzada, la investigación y la ciencia remonta sus ideas a los orígenes de los precursores ya mencionados. Esto se pone de manifiesto en nuestra actual ley 137 del 26 de junio de 1968,³ la cual regula la

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práctica de la profesión del terapeuta ocupacional en Puerto Rico. Está en uno de los incisos, lee como sigue: "Terapia Ocupacional es la disciplina que hace uso de las actividades restaurativas con el fin de conseguir que el ser humano ejerza actividades funcionales, motoras, sensoriales y perceptuales que modifiquen su funcionamiento físico psicológico y social".

En el campo de la salud mental la Terapia Ocupacional va dirigida hacia el desarrollo de patrones apropiados de conducta y la capacidad de ejecución adecuada de aquellos individuos cuyas habilidades para bregar con las tareas de su cotidiano vivir se ven amenazadas y/o limitadas. En el área de la salud mental la profesión de Terapia Ocupacional comenzando en la década de los años 60, ha hecho grandes contribuciones con la formulación y reconstrucción de diferentes marcos teóricos para el manejo de los pacientes en Terapia Ocupacional.

Una breve trayectoria y exposición de estos marcos indican lo siguiente:

I. Enfoque basado en Concepto "Ocupación o "Actividad"

Este enfoque hace incapié en los conceptos del psiquiatra, Adolf Meyer; los cuales se basan en que el hombre se mantiene vinculado a la realidad cuando se mantiene *activo* dentro del contexto de la vida diaria. Se tiene como objetivo que el paciente mantenga un ritmo adecuado de sus quehaceres diarios y capacitar al paciente para que pase un día en forma natural y sencilla. Se promueve el uso efectivo del tiempo, juegos, los trabajos manuales y la recreación como medio para que el individuo llegue a autorealizarse y asumir roles adecuados en la comunidad a tono con su espacio de vida.

Todavía hoy se toma como referencia este marco teórico el cual busca que el individuo a través de las actividades con propósito logre un equilibrio en su vida que lo aleje de la enfermedad mental. Por consiguiente, se lleva a la persona a un estilo de vida que le permita una convivencia efectiva en su medio ambiente.

Hoy en día este enfoque nos lleva hacia la prevención primaria. Orientando a la sociedad a que no sólo dirija su actividad diaria exclusivamente hacia el trabajo, sino también a participar pasiva o activamente en eventos deportivos, recreativos, culturales y hacer uso de actividades manuales y descanso.

II. Modelo Ocupación

Este modelo fue propuesto por la Trabajadora Social y Terapeuta Ocupacional, Eleanor Clark Slagle,⁴ en el cual estimulaba que el paciente se involucrara en los siguientes puntos:

1. Actividades de cuidado propio - Son aquellas concernientes al mantenimiento de una buena apariencia e higiene, trasladarse y comunicarse en forma apropiada. Actualmente se conocen estas actividades como actividades del diario vivir. Al terapeuta ocupacional le concierne este aspecto del paciente mental, que como todos sabemos muchas veces por la naturaleza de su condición se ven limitados en estas áreas. La evaluación y entrenamiento de los pacientes en las actividades del diario vivir es

una función muy importante. Antiguamente esta tarea era responsabilidad exclusiva del personal de enfermería. Hoy en día a la luz del enfoque interdisciplinario se comparte dentro y fuera del hospital esta labor. Además de que nos ubica dentro del esquema de prevención en salud mental, llevando a cabo visitas al hogar y la familia con propósitos de orientación y entrenamiento en las actividades de la vida diaria.

2. Envolverlos en conducta social (en lo cual se promueve que confraternice el paciente con sus compañeros). Actualmente a través de orientaciones grupales; de grupos de jardinería, tareas del hogar, manualidades y otros grupos, el terapeuta ocupacional interviene en esto. De esta manera puede ayudar al paciente a obtener sentido de logro y aprender a recibir aceptación y aprobación entre otras cosas.
3. Envolverse en deportes y actividades recreativas - Aquí intervienen muy directamente los terapeutas recreativos, sin embargo, el terapeuta ocupacional comparte esta función con objetivos terapéuticos específicos tales como: promover el nivel de atención, canalizar agresividad, desarrollar tolerancia hacia la frustración y promover coordinación muscular y otros.
4. Envolver al paciente en actividades con propósito - Por esto se entiende que a través de actividades científicamente seleccionadas se estimularán las destrezas, actitudes, hábitos de trabajo y juego del paciente.

Este enfoque dentro del esquema de los niveles de prevención va dirigido mayormente hacia la intervención secundaria, ya que se utiliza una vez, el paciente necesita los servicios de salud mental.

III. Enfoque Psicoanalítico

Para los años 1940-1950 la profesión de Terapia Ocupacional se vió forzada a seguir el pensamiento y la orientación de la época. El Dr. Fidler⁵ y su esposa, la Terapeuta Ocupacional, Gail Fidler,^{6,7} con sus ideas de base psicoanalítica aportan a nuestra profesión el que la conducta verbal y no verbal, sea vista como algo determinado por el inconsciente. Se toma en consideración la acción y comunicación de los pacientes para determinar el simbolismo. Por tal razón coge énfasis el uso de actividades como medio de tratamiento y el analizarlas para explorar su simbolismo. "Este se refiere al fenómeno mediante el cual se emplea una idea o un objeto para representar otro objeto o idea. Deseos inconscientes reprimidos obtienen expresión en el nivel consciente de una manera disfrazada".⁷ La forma poco estructurada y de naturaleza proyectiva de muchas actividades en Terapia Ocupacional se presta para la revelación simbólica del inconsciente.

Ejemplo:

Si a un paciente se le asigna una actividad como trabajar en barro, se observa el acercamiento del paciente hacia la tarea, su compulsión hacia la misma, su

tendencia hacia la pulcritud o al disfrute de ensuciarse, el efecto envuelto al realizar la actividad y las verbalizaciones. Todo esto puede ser indicio de fijaciones o conflictos en la etapa anal.

Actualmente antes de brindarle una actividad al paciente esta se analiza con fines de explorar su simbolismo, proveer el escape de emociones fuertes y observar como el paciente se conduce en las tareas que se le delegan. De esta manera el concepto del uso de las actividades tiene unas connotaciones más científicas.

Dentro del marco psicoanalítico el Terapeuta Ocupacional se convierte también en herramienta terapéutica, de aquí se le da mucha importancia al uso del yo o del "self". Se presume que el paciente a través de la relación que establece con la terapeuta proyecta sus actitudes, fantasías y conflictos. De igual modo el Terapeuta bajo este enfoque debe tener conocimientos de los diferentes estilos de manejo hacia los pacientes, en cuanto a los procesos intrapsíquicos envueltos y el proceso de comunicación. Este enfoque mayormente nos ubica hacia la prevención secundaria y terciaria.

IV. Enfoque Sensorial-Integrativo

Los principios neurofisiológicos entraron en vigor en 1960. A través de los trabajos de la Terapeuta Ocupacional, Dra. Jean Ayres. Este enfoque comenzó en el área de pediatría con niños con desordenes en la función neuromuscular con el siguiente principio. "La integración sensorial es un proceso neurológico que implica la habilidad para organizar, integrar e interpretar estímulos del medio ambiente. Esta habilidad se desarrolla en base a las experiencias tempranas de la infancia y son decisivas en el proceso perceptual". Cuando ocurre interrupción en este proceso, la distorsión perceptual resultante conlleva a una inadecuada interacción del individuo con el medio ambiente. Por tal razón el Terapeuta Ocupacional selecciona como medio de tratamiento los estímulos necesarios para que el paciente responda efectivamente a las demandas de tipo motor en el medio ambiente. En especial, los estímulos táctil, vestibular y propioceptivos por encontrarse que promueven el equilibrio del organismo.

Siguiendo este modelo la Terapeuta Ocupacional, Dra. Lorna King,^{8, 9} comenzó a observar en un estudio realizado en el Hospital Estatal de Arizona a mediados de la década del 70, que un gran número de esquizofrénicos crónicos presentaban un cuadro común en cuanto a: postura en forma de S (de la cabeza a los pies), patrón de caminar arrastrando los pies, inhabilidad para cruzar la línea media, inmovilidad del cinturón escapular y de la cabeza, tendencia a mantener los brazos y piernas en flexión, aducción del pulgar, falta de motivación y cara sin expresión.

Mediante estos hallazgos la Dra. King estableció la hipótesis de que algunos individuos tienen el mecanismo de retroalimentación propioceptiva defectuoso y que muchos de los disturbios que presentan estos pacientes es por la falta de integración de los sistemas táctil, vestibular, propioceptivo, auditivo y visual. Bajo este enfoque como medio de tratamiento el terapeuta brinda al paciente de una serie de ejercicios y actividades de

naturaleza amplia y no competitivas que provean la estimulación adecuada de estos sistemas para lograr así una buena integración.

Este enfoque se dirige mayormente hacia la *prevención* secundaria sin embargo, como terapeuta ocupacional podemos hacer uso de estos principios en la orientación de padres, maestros y agentes de la comunidad para que las personas desde su niñez se encaminen hacia una buena salud mental a través de una adecuada integración sensorial.

V. Enfoque de Recapitulación de Ontogénesis o Enfoque Bio-Psicosocial (Década 1960-1970)

Este enfoque fue propuesto por la Terapeuta Ocupacional, Ann Cronin Mosey,¹⁰ se basa en principios sobre el desarrollo humano en donde se dá énfasis al comportamiento desde el punto de vista neurológico y también se enfatiza la influencia del ambiente socio-cultural en el paciente mental.

Este enfoque sustenta que el ser humano tiene unas necesidades esenciales, basadas en la jerarquía de valores de Maslow, las cuales se lograrán satisfacer a través del desarrollo en secuencia de ciertas destrezas adaptativas. Estas son 7 en total y abarcan desde los aspectos perceptuales, cognocitivo, social y sexual. Son de tipo jerárquico y se adquieren de forma gradual, a través del desarrollo. El individuo tiene mejor dominio del ambiente si sigue la secuencia de estas destrezas adaptativas, ya que el desarrollo de las mismas conlleva a la expansión del yo y el dominio de su medio ambiente.^{10, 11, 12}

Aquí las modalidades del tratamiento van encaminadas hacia las actividades manuales en grupo, en las cuales el paciente aprende y sigue la secuencia de las destrezas adaptativas. Un dato importante es que estas actividades deben de simular lo más posible experiencias de la vida diaria.

Ejemplo: Una tarea de grupo en la cual los pacientes elaboren los adornos de navidad para el hospital, decoren el árbol de navidad, confeccionen las tarjetas de navidad para sus familiares, etc.

Bajo este enfoque si la persona cae en disfunción se dirige hacia la prevención secundaria. Sin embargo no se descarta la prevención primaria, puesto que una educación temprana sobre las destrezas adaptativas a lograrse a lo largo del desarrollo son indispensable para una buena salud mental.

VI. Enfoque Conducta Ocupacional o Modelo "Trabajo - Juego" (en años 70)

Este modelo ha sido propuesto por la Terapeuta Ocupacional, Dra. Mary Reilly,¹³ el cual se basa mucho en los conceptos del Dr. Adolf Meyer.

Bajo este enfoque se postula que la conducta del individuo debe ser llevada en un ciclo de vida que envuelva trabajo, juego, descanso y sueño. Esta continuidad ella la llama "Conducta Ocupacional"; en donde es importante que el individuo lleve un equilibrio en su vida en estos cuatro puntos para que así pueda llenar sus roles individuales en forma adecuada. Lo importante

bajo este esquema es que el individuo aprenda a organizar su vida.

Ella opina que la hospitalización prolongada e innecesaria de los pacientes psiquiátricos no sólo atrofia los músculos, sino la mente. Visualizaba la hospitalización lo más corta posible, ya que estima que el ambiente de hospitalización no facilita la conducta ocupacional.

Este enfoque está a tono con la corriente moderna de que el paciente se integre a la comunidad lo más pronto posible después de una breve hospitalización, de ser ésta necesaria. Así también se manifiestan Liberman y Foy en un estudio publicado en el "Psychiatric Annals" de agosto de 1983.¹⁴ De igual manera puede ser un enfoque de prevención primaria en el área de la salud mental, ya que educando a la comunidad en términos de una buena organización del tiempo y hacia un estilo de vida bajo el ciclo de trabajo, juego, descanso y sueño se promueve la salud mental. A su vez este modelo puede aplicarse a la industria, programas educativos o de enseñanza superior entre otros.

Los marcos teóricos descritos guardan relación los unos con otros y sobre sus fundamentos descansan el proceso de intervención en Terapia Ocupacional en salud mental.

Los diferentes marcos teóricos van dirigidos hacia los "componentes de ejecución",¹⁵ que son las diferentes áreas de funcionamiento del hombre que a saber son las siguientes: sensorial integrativo, psicosocial y cognitivo. Así como a las destrezas básicas de vida independiente.

El trasfondo histórico señalado, las bases teóricas expuestas y nuestra colaboración por tantos años en el equipo interdisciplinario de tratamiento nos hace pensar y señalar la valiosa aportación de esta profesión en el campo de la salud mental. Puesto que se ha comprobado que la actividad con propósito es un medio efectivo de tratamiento. Esto acompañado en algunos casos con el uso de medicamentos y otras aportaciones de profesionales de la salud redundaría en una intervención completa y más realista para el paciente mental dentro de la realidad histórica y sociocultural del Puerto Rico de hoy.

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What can you do for hypertensives like Don S?

New patient

Workup at 56 shows a systolic of 162 mmHg, diastolic of 100 mmHg.

Dislikes taking medication

Prior to last year, never sick in his life. Hates the thought of yet another medication.

Coexistent ulcer

Previous physician put him on cimetidine.

Loves food

But often eats on the run... vows to be more careful.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

ONE TABLET A DAY TENORMIN® (atenolol)

For Don S...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol) with caution—see OVERDOSAGE. Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacu-

lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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STUART PHARMACEUTICALS

Division of ICI Americas Inc.

Wilmington, DE 19897

STR-2229

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Don S represents 899 black patients between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even in Don S's racial and age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Compatible with cimetidine and ranitidine

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when administered concomitantly with cimetidine or ranitidine.³⁻⁵ This compatibility of TENORMIN with today's widely prescribed H₂ receptor antagonists makes it a logical choice for hypertensives like Don S who are under treatment for a coexistent ulcer.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁶ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Don S...and virtually
all your hypertensive patients

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary
of prescribing information.



STUART PHARMACEUTICALS



Sonography Quiz

Bernardo Marques, M.D.*
Manuel R. Pérez, M.D.

This 69 year old diabetic male presented with a two months history of increasing pain and swelling of the left testicle. No history of trauma or previous similar episode was elicited. Physical examination of the scrotum was very limited because of severe tenderness of the left scrotal area.

Water path sonogram of the scrotum was performed (Fig. 1 and 2).

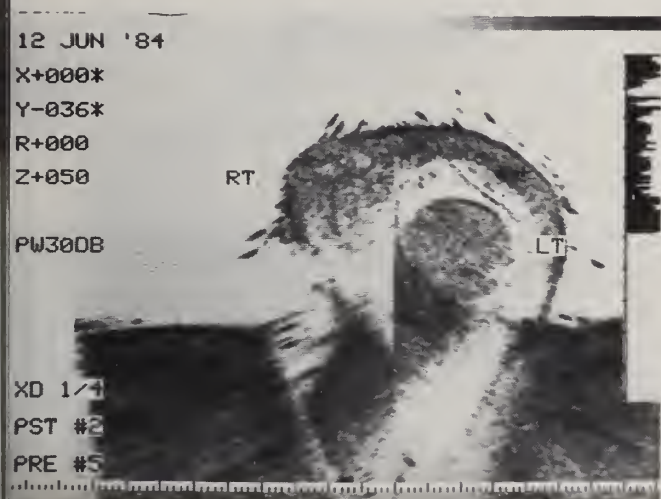


Fig. 1. Marked thickening of the skin of the scrotum on the left is noted. A hydrocele-like fluid collection surrounds the left testicle. The sonographic texture of the left testicle is uniform.

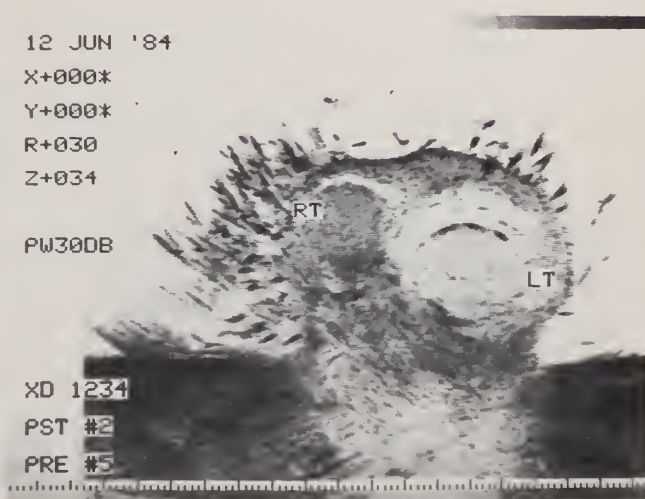


Fig. 2. Rotation view obtained to demonstrate both testicles through their center shows the left testicle to be distinctly hypolucent as compared to the right. Again the skin thickening and fluid collection surrounding it is evident.

1. What are the salient sonographic findings?
2. What is your diagnostic impression?

- a) Hydrocele
- b) Testicular Torsion
- c) Testicular Tumor
- d) Epididymo-orchitis
- e) Testicular Abscess

*Director Radiology Department, Hospital Pavía, Sanaturce, Puerto Rico.

Our diagnostic impression was: **Epidydymoorchitis** with accompanying hydrocele.

The patient underwent surgical exploration of the left scrotum, which revealed a left testicular abscess containing 30cc of foul smelling pus.

Testicular abscess is a rare condition. In its presence adequate palpation of the scrotum is not tolerated by the patient. In this and other inflammatory conditions of the scrotum automated waterpath sonography provides excellent detail without patient discomfort. If rotational filming capability is present, comparison of echo-texture of both testicles at a similar level can be easily done.

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Charles D. Johnson, MD, FACC

Questions

1. What are the cardiac arrhythmias?
2. What are the primary arrhythmia and cardiac syndrome?
3. What electrophysiological principles are demonstrated?
4. What are the differential diagnoses?

Figures 1-A, 1-B, 1-C

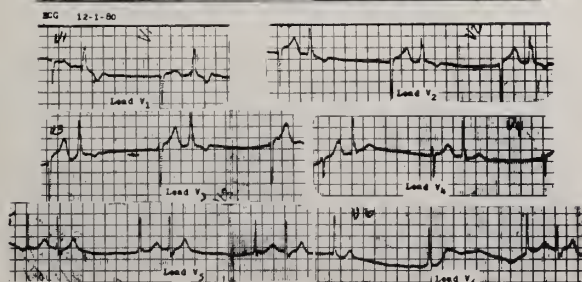
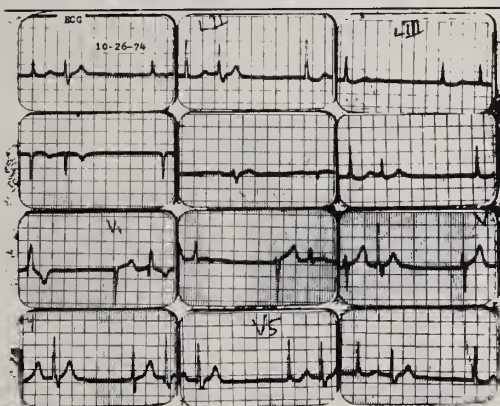
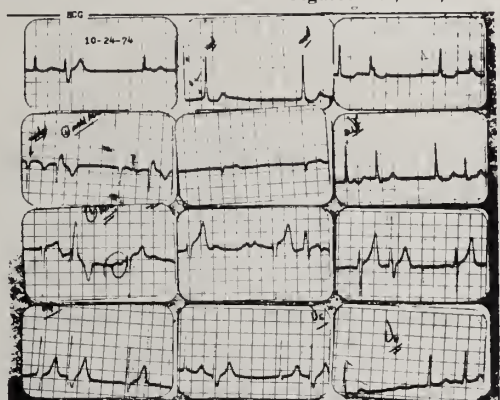


Figure 2

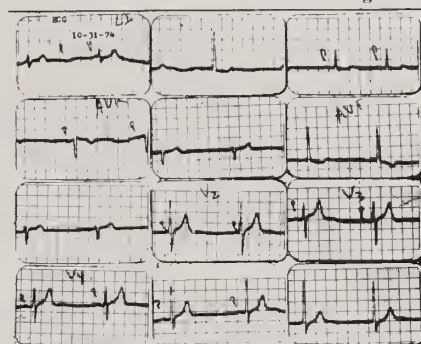


Figure 3

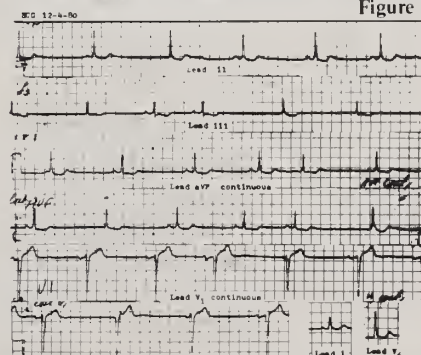


Figure 4

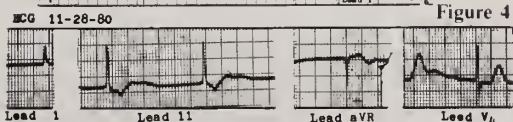
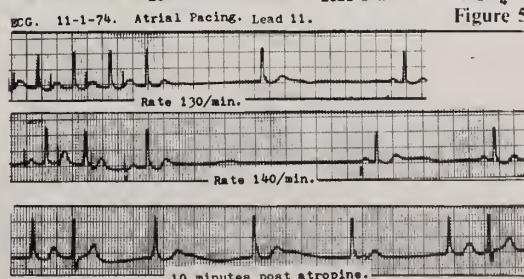


Figure 5



Answers

Figures 1 A, B, C. Sick Sinus Syndrome (SSS). Marked sinus bradycardia and arrhythmia, sinus arrest or 2:1 sinoatrial (SA) block (as 31 per minute is too slow for sinus bradycardia).

Escape-capture Bigeminy (ECB) secondary to SSS. Often sinus capture of ventricles (VCBs) with first degree atrioventricular (AV) block and phasic aberrant ventricular conduction, phase 3 block, of right bundle branch block (RBBB) type, or normal ventricular conduction. Ailing or sluggish AV junction - AV node disease. Incomplete AV dissociation (AVD).

P rate 31-64; P-P cycle 933-1960 ms; coupling intervals 520 ms for the RBBB VCBs, 560 ms or more for the VCB without aberration; R-P interval 200-400 ms with aberration, 420 ms without; P-R intervals 0.15-.40 S; escape intervals 1000-1680 ms.

Figure 2. Sinus bradycardia. Isorhythmic AVD. Incomplete RBBB. Axis more to right. P-P cycles 980-1450 ms; R-R cycles 1000-1440 ms.

Figure 3. Sinus bradycardia and arrhythmia (minimal P rate 31).

Wandering atrial pacemaker. Junctional escape beats (JEB), minimal rate 36.6. AVD.

Figure 4. Junctional escape rhythm, which prevented ECB (R-R cycle 1240 ms or more), with retrograde atrial conduction.

Figure 5. Atrial pacing revealed a prolonged atrial recovery time, maximum 3100 ms, and a corrected recovery time of 1700 ms, confirming the obvious SSS. The AV junctional recovery time was delayed to 3000 ms, corrected 1600 ms, confirming the AV node disease. Post-atropine rate 43 per minute.

Discussion

The SSS in this patient set-up the ECB, a form of incomplete AVD, because the conducted sinus cycle greatly exceeded the escape cycle plus the refractory period (rp) of the escape beat.

R-P intervals of 100 ms or less did not permit P wave conduction because of physiological refractoriness, while R-P intervals of 420 ms or longer allowed normal AV and ventricular conduction. Intermediate R-P intervals between 100 and 420 ms produced VCBs with variable P-R intervals (normal to first degree AV block depending upon the relative rp of AV node) and variable RBBB morphologies (incomplete to complete); the R-P intervals were inversely proportional to the P-R intervals. Aberrant ventricular conduction is determined by prematurity (Phase 3 aberration), unequal refractoriness of bundle branches (BB) and the length of the preceding R-R cycle (the longer the junctional escape interval, the longer is the subsequent rp). The rp of the right BB is longer than that of the left BB.

Differential Diagnosis

The VCB of the escape-capture pair must be differentiated from other forms of bigeminal rhythm such as: 1) an atrial or junctional premature beat, which manifests an early diastolic beat but one associated with a premature ectopic P wave; 2) a ventricular premature

beat (VPB) which is often mistaken for an aberrantly conducted VCB; VPBs are also favored by a preceding long-short cycle sequence; however, a VPB would not of course be associated with a conducted sinus impulse; and 3) importantly, a junctional reciprocal (RB) or echo beat which is a form of reentry. This would manifest as a premature retrograde P wave (inverted in leads II, III, aVF) or atrial fusion (P sandwiched between the JEB and the VCB); the R-P interval is usually 200-500 ms and is inversely proportional to the P-R interval of the RB. An aberrantly conducted RB would especially mimic an aberrantly conducted VCB.

AV node disease was present also in this patient; the corrected junctional recovery time was greater than 1460 ms.

This case demonstrated four possible sequelae of a JEB: 1) AVD terminated by VCB; sinus rate slower than escape rate, absence of retrograde conduction; 2) retrograde activation of the atria by the escape beats pre-empts the next sinus impulse; 3) isorhythmic AVD; and 4) resumption of sinus rhythm which pre-empts the second escape, the sinus rate is faster than the escape rate.

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De la Cruz, Juan de Dios, MD - Universidad Autónoma de Santo Domingo, República Dominicana; 1964. Especialidad: Cirugía. Ejerce en Caguas.

Hoyos Preccas, Guillermo, MD - Universidad de Madrid, España; 1966. Especialidad: Psiquiatría. Ejerce en Guaynabo.

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NEW ACNE DRUG USERS SHOULD BE DEFERRED AS DONORS

In a recent memorandum from Elaine Esber, MD, of the Public Health Service, all establishments collecting blood, blood components and source plasma were advised to defer donors who are taking the new drug, Accutane (isotretinoin/Roche; 13-*cis*-retinoic acid). The drug has been shown to be a potent teratogenic agent and appropriate warnings are included in the labeling and packaging insert. The drug is used to treat severe recalcitrant cystic acne.

"It has come to our attention that if a donor who is receiving Accutane gives blood, and the donated blood is transfused into a patient who either is or soon becomes pregnant, there may be a risk to the developing fetus because of Accutane in the transfused blood. The blood recipient could also suffer significant side effects," the memorandum reads.

"Although there are quantitative data available with respect to the period of time between receipt of the last dose of Accutane (isotretinoin) and the clearance of Accutane from the blood, it is not known what levels can be considered non-teratogenic. In addition, it is known that the clinical effects of Accutane can persist after the drug has been discontinued, but it is not known whether this reflects the presence of low drug levels in the circulatory system."

For these reasons, the Public Health Service is advising that any donor taking Accutane be deferred for at least one month from receipt of the last dose.

ARMOUR TO MARKET NEW TREATMENT FOR MILD HEMOPHILIA

Armour Pharmaceutical will begin to market an intravenous form of the synthetic antidiuretic hormone DDAVP (adeamino 8-d-arginine vasopressin), used to treat mild and moderate hemophilia A and von Willebrand's disease, type I. The Food and Drug Administration approved Armour's application to market the drug. The DDAVP is manufactured by Ferring AB, Malmo, a Swedish company. The trade name will be Stimate. It represents, according to Armour, an effective and safer treatment alternative to Factor VIII concentrate.

STUDY GROUP RELEASES STATEMENT ON ANTI-HBc TESTING

On March 6, 1984, the study group formed subsequent to the December 1983 meeting of the FDA Blood Products Advisory Committee met to discuss the issue of testing potential blood and/or plasma donors for core antibody to hepatitis B (anti-HBc). Membership of the study group consisted of representatives of the commercial and non-commercial fractionation industry, the plasmapheresis community, nonprofit blood collection and processing organizations and the Food and Drug Administration. The purpose of the meeting was to review all aspects and ramifications of the use of testing for anti-HBc as an additional means of determining whether potential donors were members of high risk groups associated with acquired immunodeficiency syndrome (AIDS). Although a full report of the study group's deliberations and conclusions will be furnished to the Food and Drug Administration in the near future, it was felt that an interim statement should be made available at this time.

The study group was divided in its position on testing for anti-HBc as a means of identifying AIDS high risk group members, with the majority believing that such testing was not appropriate for that purpose. However, members of the majority group indicated that they would likely be compelled to follow suit if any of the organizations represented initiated anti-HBc testing programs. The report to be prepared will contain certain position papers summarizing the majority and minority opinions on this issue. It was clearly recognized by the study group that a positive finding of anti-HBc in an individual was not necessarily indicative of AIDS or the future development of the disease state. Rather, it was viewed as a possible mechanism of identifying high risk group members, a number of whom are positive for this serologic marker. It was the prevailing opinion of the study group that if testing programs for anti-HBc are employed, they should not be confined to the plasma donor population but should extend to whole blood donors as well.

There was unanimity on two additional issues that the study group addressed. First, the study group recommended the initiation of a pilot study in at least two metropolitan areas to ascertain the effectiveness of allowing plasma donors to privately provide a written indication as to whether their plasma should be used in manufacture of products used in hemophilia treatment, analogous to the system currently utilized by the New York Blood Center in whole blood collection. Secondly, the study group recommended that pilot studies involving testing for B-2 microglobulin levels be designed, since the presence of this analyte appears to offer a higher degree of correlation with prodromal or active AIDS.

AMERICAN COLLEGE OF PHYSICIANS



ACP EVALUATES ENDOSCOPIC SCLEROTHERAPY OF ESOPHAGEAL VARICES

A recommendation on the use of endoscopic sclerotherapy for esophageal varices was published by the American College of Physicians (ACP) in the April issue of the *Annals of Internal Medicine*.

The statement is issued as part of the College's Clinical Efficacy Assessment Project (CEAP), by which the ACP evaluates the safety and efficacy of medical tests, procedures and therapies and makes recommendations on their appropriate uses.

Traditional medical means of controlling bleeding esophageal varices include the use of vasopressin, a hormone that stimulates contraction of the arteries; and balloon tamponade. Surgical treatment includes the use of various types of shunts, devascularization, and stapling. In endoscopic sclerotherapy, an esophagoscope is passed down through the esophagus to the affected area and a sclerosing agent injected into or around the varix to control the bleeding. A series of such procedures often is

necessary to obliterate all varices.

According to the ACP statement, sclerotherapy is the procedure of choice in patients whose varices have not responded to medical means of control and who are not candidates for surgery. In addition, it continues, the procedure may be useful as a temporizing measure to control acute bleeding until surgery may be performed.

The College found endoscopic sclerotherapy to be associated with moderate risk, particularly when repeated injections are used in an acute setting. Pulmonary and gastrointestinal complications were found to occur in 10% to 15% of patients, and procedure-related deaths in about 1% of patients.

The paper stresses that important questions remain unresolved relating to the type of esophagoscope used; the type and volume of sclerosing agent used; the type, number, and frequency of injections; long-term consequences; systemic side-effects of sclerosing agents; the frequency of follow-up evaluation; and the role of adjunctive supportive medical therapy. The College recommends the performance of multicenter, randomized controlled trials to address issues of survival, to permit comparison with alternative surgical therapies, and to evaluate the procedure's use as a temporizing measure and as a preventive measure when varices have not yet bled.

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ORAL ACYCLOVIR EFFECTIVE TREATMENT FOR RECURRENT HERPES

Patients with recurrent genital herpes may find relief from symptoms and reduce their risk of transmitting the disease by taking oral acyclovir, according to a new study reported in the April 27 issue of JAMA.

"The antiviral agent acyclovir offers a genuine ray of hope to patients with herpes—both as an effective treatment and as a potential prophylaxis," say William L. Whittington and Willard J. Cates, Jr., MD, MPH, of the Centers for Disease Control, Atlanta, commenting editorially on the study. They add that oral acyclovir taken early in the course of genital herpes infections reduces viral shedding, shortens lesion duration and speeds eventual healing.

Conducted by Richard C. Reichman, MD, of the University of Vermont College of Medicine, and colleagues from six other institutions, the collaborative study included 377 patients with recurrent genital herpes; 212 were treated by physicians within 48 hours of a recurrence and 165 initiated therapy themselves as soon as they noticed symptoms of a recurrence.

Half the patients in each group received 200 mg of acyclovir five times daily for five days; the other half received placebo. In both groups, "the duration of virus shedding and the time to crusting and healing of lesions were shorter among acyclovir recipients than among placebo recipients," the researchers say. Results were significantly superior among the patients who administered their own therapy as soon as possible after onset of a recurrent episode. The study "establishes orally administered acyclovir as the first well-documented modality to affect both the virological and clinical course of genital herpes," according to the researchers.

They point out that, in addition to providing relief for patients with herpes, acyclovir shortens the duration of viral shedding and can thereby reduce the likelihood of transmission of the disease. As many as 35 percent of the sexual partners of people with recurrent genital herpes have intercourse during the time of the recurrences and are therefore at risk of contracting herpes, according to the researchers.

Two major concerns are associated with the long-term use of acyclovir: the potential for developing viral resis-

tance to the drug and the possibility of its toxicity. So far, there is no conclusive evidence of either resistance or toxicity, but the drug has not yet been used to treat large numbers of patients over long periods of time. The CDC researchers conclude, "given concerns about the potential for developing viral resistance and for experiencing toxicity not yet observed, decisions on the use of the agent have to be carefully weighed against clinical benefit."

The CDC researchers also note that, patients taking daily acyclovir in other studies reported fewer recurrences of genital herpes, but that unfortunately, when the drug was withdrawn, there was no lasting effect on the rate of recurrences. They add, "we would certainly advocate that clinicians make themselves aware of the real benefits of this therapy, realizing, however, that it is not a cure."

STUDY DOCUMENTS HAIR REGROWTH

Hair regrowth was seen in 25 of 48 patients participating in a study of the effectiveness of 1 percent minoxidil solution. The study is reported in the April *Archives of Dermatology*. Virginia C. Weiss, MD, and colleagues from the University of Illinois in Chicago say that the hair regrowth was cosmetically acceptable in 11 of the 25 patients responding to therapy. Minoxidil is a potent peripheral vasodilator that might stimulate hair growth by effecting blood flow, the immune system, or by direct effect on hair follicles, the researchers say.

NEW NIH RECOMMENDATIONS FOR HIGH BLOOD PRESSURE CONTROL

New recommendations for the detection and treatment of high blood pressure are offered by the National Heart, Lung and Blood Institute in the May *Archives of Internal Medicine*.

The recommendations represent a follow-up to a 1980 NIH report and reflect advances made in detection and treatment since then. High blood pressure, or hypertension, is associated with a number of clinical conditions, including stroke and heart disease.

Since publication of the first report, "several events have occurred that affect successful management of hypertension," the new report notes. These include "publication of major clinical trial results, introduction of new antihypertensive agents, evidence concerning effectiveness of nonpharmacologic treatment, and further analysis of the epidemiologic data-base relating blood pressures with the risk of premature morbidity and mortality."

The report points out that patients should understand that a single elevated blood pressure reading does not constitute a diagnosis of hypertension, but a sign for further observation. "The diagnosis for adults is confirmed when the average of two or more diastolic BPs on at least two subsequent visits is 90 mm Hg or higher, or when the average multiple systolic BPs on two or more

subsequent visits is consistently greater than 140 mm Hg."

Patients with a diagnosis of hypertension should be encouraged to adopt nonpharmacologic approaches as definitive intervention and, they should add drug therapy, if needed, the report says. The first goal is to reduce weight. "Weight reduction by caloric restriction often results in a substantial decrease in BP, even if the ideal body weight is not achieved."

The report also recommends restricting dietary sodium to an equivalent of 2 grams of sodium or 5 grams of salt per day. Alcohol should be restricted to less than 4 oz hard liquor, 16 oz of wine or 48 oz of beer per day. Levels of blood cholesterol should be reduced when feasible and avoidance of smoking should be encouraged. Finally, the report recommends a regular exercise program of walking, jogging or swimming as an aid to controlling both weight and blood pressure.

While controversy remains about the use of antihypertensive drugs, the report says, "this should not be a reason to withhold antihypertensive treatment from patients 50 years of age and older."

The report also recommends that special treatment be used for defined at-risk patients, including black Americans, patients with cerebrovascular and coronary artery diseases, surgical candidates, patients with diabetes mellitus, elderly and young patients, pregnant women, and patients with kidney impairment.

NEW APPLICATION FOR GROWTH HORMONE SEEN

Short children who are not generally considered deficient in growth hormone (GH) may, in fact, be clinically deficient and benefit from replacement therapy.

Such children may have a growth hormone secretion abnormality, according to a new observation by Bessie E. Spiliotis, MD, of the National Institutes of Health, and colleagues. Their study, described in the May 4 issue of JAMA, included 45 children, seven with short stature who normally would not be considered GH deficient, 17 who clearly were GH deficient, and 22 controls. The researchers report that "as with GH-deficient children, the group with GH neurosecretory dysfunction more than doubled their growth velocity after replacement therapy with exogenous human GH during the first year of treatment."

In the study, blood samples were taken from all children every 20 minutes during a 24-hour period to measure GH secretion. This screening method disclosed that the seven short children who initially had normal provocative GH test results were, in fact, partially GH deficient because of secretory abnormalities. These children were treated with two units of human GH three times a week for at least six months, and growth velocity increased in six of the seven patients. The researchers note that, during the past 25 years, treatment with human GH has been restricted to only the most profoundly affected children, but that through recombinant DNA technology, sufficient quantities of GH will be produced

so that many more children can be treated. Their study suggests that "there is a spectrum of GH secretory abnormalities from absolute deficiency to an intermittent irregularity in GH secretion." They add, "more studies are necessary to determine the mechanisms involved and the number of patients that would ultimately benefit from exogenous human GH, especially in a climate of abundant supply."

Commenting editorially, William H. Daughaday, MD, of Washington University School of Medicine in St. Louis, points out that few physicians would have access to metabolic wards where sampling every 20 minutes would be possible, so the diagnosis of GH neurosecretory dysfunction is limited. Also, he says the long-term results of treatment of partial deficiency of GH secretion and its effect on normal children are unknown. He concludes that "we urgently need more practical methods of measuring partial deficiency of GH secretion," and that "until much more information is available, physicians should refrain from prescribing such treatment."

SOME FOODS CAN BE FATAL FOR CHILDREN

Hot dogs are the food most often associated with fatal childhood asphyxiation, according to a new study by Carole Stallings Harris and colleagues of Johns Hopkins University, Baltimore.

Writing in the May 14 issue of JAMA the researchers point out that round, pliable food products are most often involved in fatal choking accidents among youngsters. The researchers studied records of 103 infants and children whose deaths were attributed to specific foods. Hot dogs, candy, nuts or grapes accounted for more than 40 percent of the deaths; hot dogs alone accounted for 17 percent.

They also found that the highest incidence of childhood food asphyxiation was among 1-year-olds, and that the types of food cited varied according to age. Hot dogs, apple pieces, and cookies or biscuits caused half the deaths in infants younger than 12 months. For 1-year-olds, many foods were cited; carrots and, again, hot dogs most often. Grapes and peanuts were the most frequent causes of choking among 2-year-olds, and for 3-year-olds, the total number of food deaths dropped, but seven of the ten deaths were caused by hot dogs.

Federal regulations have been established for nonfood products that present choking hazards for infants and young children, but no similar regulations have been set for foods, the researchers say. They add, "The number of deaths from food asphyxiation is of the same magnitude as the number of childhood deaths from poisoning, which in recent years was about 75 deaths annually."

The researchers recommend preventive measures such as product modification, warning labels and dissemination of information on high-risk foods to reduce the incidence of childhood food asphyxiation. The article is accompanied by a prototype label supplied by Giant Food, Inc.

SABIN OUTLINES PLAN FOR ELIMINATING MEASLES

Albert B. Sabin, MD, and colleagues have found through a comparative study of measles vaccines that some forms and methods of administering them are far more effective for immunizing infants. The findings promise global elimination of measles.

Writing in the May 11 issue of JAMA, the researchers explain that measles can be a serious and sometimes fatal disease, especially during the first year of life for children in developing countries. One problem in protecting these infants, according to the researchers, is that those aged 4 to 6 months may respond to vaccines differently because of varying levels of residual maternal antibody. In the study, they sought to find the lowest concentration of virus that would produce the desired immunity so they could suggest methods of vaccinating the largest number of infants in the shortest possible time.

The researchers note that there are annual programs in many countries for the administration of oral polio vaccine, and they suggest that aerosolized measles vaccine could be included in these programs. They add, "with proper organization and coordination, [this strategy] has the potential of controlling measles within a single year instead of after decades."

The researchers studied the effectiveness of two vaccines, chick embryo fibroblast (CEF) and human diploid cell (HDC), among infants and children in Nuevo Leon, Mexico. They found the HDC vaccine to be superior in infants aged 4 to 6 months but suggest one factor may have been the high sugar content of the CEF vaccine. They also found the two methods used to test for immunity measured different antibodies that develop and persist in different ways in 4- and 5-month-old infants. One concern the researchers have is that the vaccine needs to be kept cold to be effective. The nebulizer they used was kept in crushed ice, which is a rare commodity in many warm countries.

In an accompanying editorial, Robert W. Amler, MD, and colleagues of the Centers for Disease Control, Atlanta, suggest that larger clinical trials are needed to work out the details for successful immunization campaigns in developing countries. However, they recognize the value of these study findings: "Dr. Sabin and his colleagues have demonstrated important determinants of the immunogenicity of vaccines and the kinetics of the immune response in an age group for whom successful vaccination is life-saving." They add, "Their observations bring us one step closer to eventual global eradication of measles."

The findings of Sabin and colleagues are the second part of a larger study of aerosolized measles vaccine. The findings of the first part, which appeared in a May issue of JAMA, established that aerosolized measles vaccine was more effective than subcutaneously injected vaccine for immunizing infants with or without maternal antibody.

PELVIC INFLAMMATORY DISEASE INCREASING: PILL MAY HELP

The number of women hospitalized for pelvic inflammatory disease (PID) registered a measurable increase between 1975 and 1981, according to a report in the May 18 issue of JAMA.

Researchers A. Eugene Washington, MD, and colleagues from the Centers for Disease Control in Atlanta, who conducted the study, say the trend may be attributed to three distinct causes: the liberal sexual behavior of the baby-boom generation, the increased incidence of sexually transmitted diseases and the decline in the use of barrier contraceptives. The researchers add that ectopic pregnancies and infertility, possible unfortunate consequences of PID, also increased during the 1970s.

During the seven years of the study, an estimated average of 267,200 women were hospitalized annually for PID, with hospitalization rates averaging 5.3 per 1,000 women, according to the report. The incidence of hospitalization for PID was highest among women aged 25 to 34 years and was higher among divorced or separated women than among married or single women, the researchers say. They add that nonwhites had a higher rate of hospitalization for the disease, but that the rate for whites was increasing.

Sexually transmitted organisms other than *Neisseria gonorrhoeae* are now recognized as important causes of PID, and the intensity of symptoms is apparently related to cause, the researchers say. "Salpingitis associated with gonococcal infection causes more severe symptoms, while that associated with nongonococcal infection is clinically more indolent," they add, suggesting these less severe forms may go untreated and later require hospitalization.

In a related article, Lars Svensson, MD, and colleagues of the University of Lund in Sweden, suggest there may be a correlation between the severity of salpingitis and the type of contraceptives used at the time of onset of illness. Their study of 546 women with salpingitis, found that inflammation of the fallopian tubes was significantly less severe in those who used oral contraceptives than in those who used other methods. They note that results from other studies indicate that the relative risk for acute salpingitis is increased if a woman uses an IUD, but it is decreased if she uses oral contraceptives.

The Swedish researchers conclude that since the severity of inflammation affects the future fertility of the woman, oral contraceptives may be preferred for those woman at high risk for acute salpingitis.

NEW HEPATITIS B VACCINE MADE BY RECOMBINANT DNA

A vaccine for hepatitis B, produced by recombinant DNA, has been tested and proved effective, according to a report in the June 1, 1984 issue of JAMA.

Edward M. Scolnick, MD, and colleagues, of the Merck Institute for Therapeutic Research, believe their study is the first to use such a vaccine in humans. The researchers say that another vaccine for hepatitis B has been shown to be safe and effective, but it uses hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of the disease, which means its supply is limited by available sources of suitable plasma. They explain that with recombinant DNA, the supply can be maintained, and the vaccine is pure and free of any extraneous living agent that might be present in the starting plasma. The unjustified fear of contracting AIDS from donor plasma has slowed the acceptance of the current vaccine, they say.

The new vaccine was produced by a recombinant strain of the yeast, *saccharomyces cerevisiae*. Supplies of vaccine were purified by two different methods and given to two groups of healthy volunteers, 15 and 22 patients respectively. One vaccine seemed to cause much less soreness at the injection site, but both yielded similar results for immunity. Each subject received 10 ug of HBsAg at zero, one, and six months. By one month, 27 to 40 percent of the vaccinees had antibody and by three months, 80 to 100 percent were antibody positive. Immunity increased markedly after the booster dose at six months. The results are comparable to those of earlier studies using vaccine derived from human plasma.

None of the 37 patients experienced any serious adverse effects from the vaccine, the researchers add.

Hepatitis B is a major public health problem worldwide, the researchers say, and chronic liver disease, cirrhosis and primary hepatocellular carcinoma are now recognized as complications of the disease. They note that liver cancer attributable to hepatitis B infection is a leading cause of cancer among males in some areas of Asia and Africa. There are 1 million hepatitis B carriers in the United States and 200 million worldwide. "Since there is no effective treatment for hepatitis B infection, prevention is essential," the researchers say.

In a related JAMA Medical News story, Marsha Goldsmith quotes Edward M. Brandt, MD, assistant secretary for health of the Department of Health and Human Services: "The recommendation that persons at high risk of [HBV] disease receive this...vaccine has had little impact." This may be because of the high cost, the unknown duration of immunity, and the fear associated with the plasma-derived vaccine. The promise of the new recombinant DNA vaccine is that it will be as effective and less expensive than plasma derived vaccine, allowing large-scale immunization.

VIRAL CULTURE AVERTS NEONATAL HERPES

Weekly viral cultures for pregnant women with recurrent genital herpes can reduce the incidence of neonatal infection, according to a report in the June 1 issue of JAMA.

The researchers, Nancy J. Binkin, MD, MPH, and colleagues, of the Centers for Disease Control in Atlanta, examined the benefits, risks and costs of viral culture

screening for women with recurrent genital herpes. They estimate that in a cohort of 3,600,000 women, screening would avert 11.3 neonatal deaths and 3.7 cases of severe retardation, but that 3.3 women would die as a result of cesarean deliveries necessitated by culture results. They add that weekly cultures would diagnose 25 percent of the women with subclinical recurrent infection at delivery. An additional 30.6 cases of neonatal herpes could be avoided each year in the United States they say, with the cost per case approximately \$1.8 million.

The researchers point out that cesarean delivery prevents transmission of infection from mother to offspring in most cases, but also poses a greater risk to the mother and is more costly. Many potential cases of neonatal infection can be prevented if thorough histories and physical examinations are done, they say. Yet some women transmit the infection to their infants while showing no symptoms of the disease. Thus, the principal objective is to provide culture screening for women at high risk: those with a history of recurrent genital infection, those with active disease during the pregnancy, and those whose sexual partners have genital herpes.

A major problem with culture methods is the need for a minimum two-day incubation period. The delay can lead to a cesarean birth when the virus actually is no longer present, or a natural birth when viral shedding develops just before labor begins. "The prevention of neonatal herpes among newborns of women with recurrent genital herpes is likely to remain a problem until a rapid and accurate diagnostic technique that can be performed at the time of labor is developed," the researchers say.

In an accompanying editorial, Janet R. Daling, PhD, and Marsha E. Wolf, MD, of the University of Washington School of Public Health, point out that some costs were not considered by the CDC researchers. These include costs of therapy and special education or institutionalization for mentally handicapped children. They also say that the rate of cesarean deliveries in women with herpes is reported to be as high as 54 percent, suggesting that physicians are not culturing the women or that they are performing cesarean deliveries despite negative culture results. Finally, they suggest that the costs of screening and possible cesarean deliveries may be viewed as worthwhile increments, since the delivery of a healthy infant should be the foremost concern of both the mother and the physician.

BOXING OR HEAD BLOWS SHOULD BE BANNED

Either boxing or blows to the head should be banned, says George D. Lundberg, MD, editor of the *Journal of the American Medical Association*.

His recommendations accompany two new reports in this week's *Journal* that describe cases of brain damage among boxers. They follow major studies on the dangers of boxing that appeared in a January 1983 issue of the *Journal*, published in the wake of the ring-injury death of Duk Koo Kim. Since then, 11 more boxers have died as a

result of boxing injuries, Lundberg says, citing *Ring* magazine statistics. "Untold hundreds have suffered brain damage," he adds.

One new study by Ira R. Casson, MD, of the Long Island Jewish-Hillside Medical Center, Jamaica, New York, and colleagues included the neurological examination, EEG, CT scan, and neuropsychological testing of 18 former and active boxers. Researchers found 87 percent of the professional boxers (13 of 15) had definite evidence of brain damage and all including amateurs, had abnormal results on at least one of the neuropsychological tests, that measured short-term memory. Symptoms of neurological dysfunction would not normally be expected among the study subjects, the researchers say. All had secondary or college education, held responsible jobs and had no history of substance abuse.

Casson and colleagues stress that these were otherwise healthy men who had overall successful boxing careers and relatively few knockouts. The fact that 87 percent of the professional boxers showed unequivocal evidence of cerebral dysfunction suggests that existing medical controls and safety measures are not effective in preventing chronic brain damage.

In a related report, Peter W. Lampert, MD, of the University of California, San Diego, School of Medicine, and John M. Hardman, MD, of Honolulu's University of Hawaii School of Medicine, question the logic of proposing regulations aimed at preventing injury when the purpose of boxing is to inflict injury. They describe the devastating damage caused by blows to the head: "Professional boxers are capable of delivering blows with forces that may exceed 100 g. Such blows applied to the movable head cause the soft brain to glide and swirl within the skull, tearing vessels and nerve fibers." Also, they say, data suggest that repetitive subconcussive blows are more damaging in the long run than occasional knockout blows.

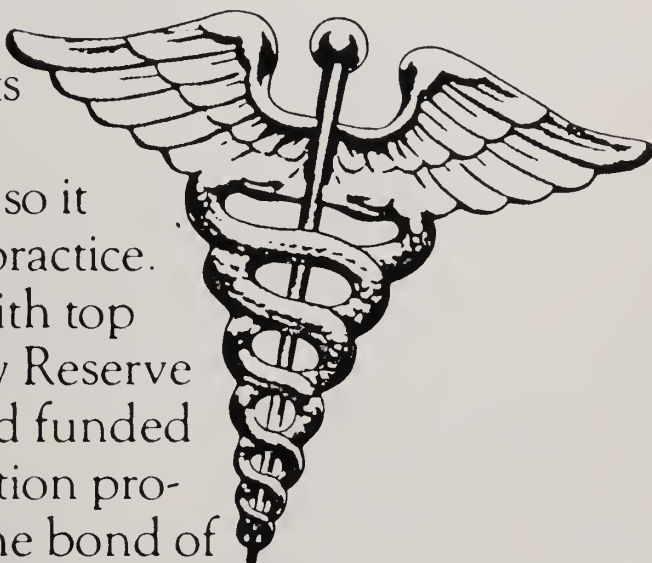
Depending on the angle and acceleration, blows to the head can cause such problems as tearing of connecting veins and vessels within the brain, severing of axons in the white matter, damage to the carotid and brain stem, and retinal detachment, the researchers add. These injuries can cause serious or fatal hemorrhage, swelling or reduced blood flow. "There can be little doubt that boxing can induce permanent damage of the brain, which may lead to typical clinical and structural alterations known as dementia pugilistica."



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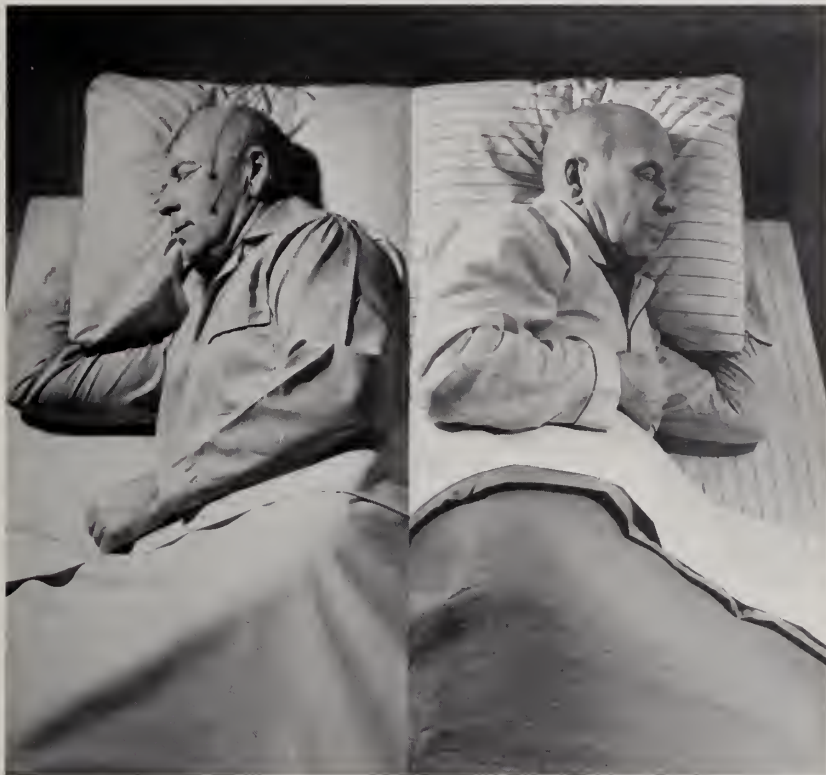
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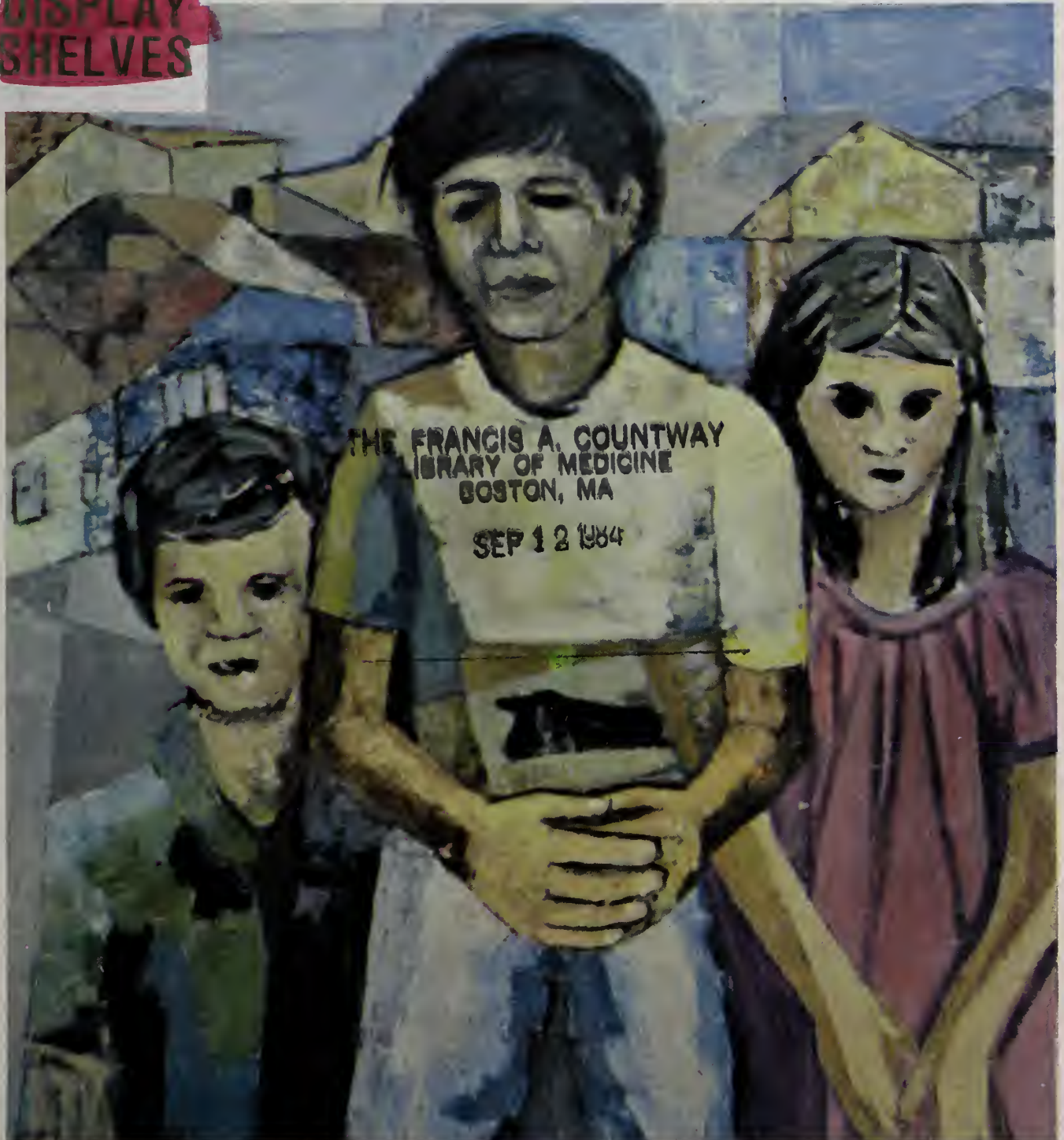


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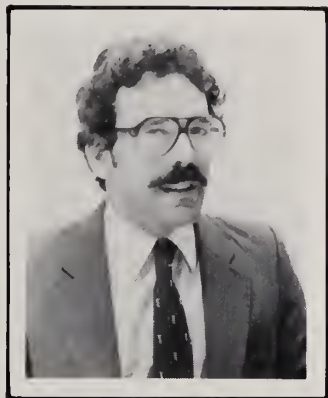
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Columna del Editor



En este número aparece la segunda Jornada de Cardiología que confiamos seguirles ofreciendo según se vayan celebrando. También reaparecen los "Medical Aspects of Nutrition" que luego de una breve interrupción esperamos continuar publicando cada mes. En el Foro de Medicina Nuclear se presenta un caso a propósito del cual los autores nos informan su experiencia con una técnica diagnóstica no-invasiva que merece la más seria consideración en el diagnóstico del sangramiento del tracto gastrointestinal bajo. La reproducción del artículo sobre las enfermedades y probables causas de muerte de Wolfgang Amadeus Mozart, desde el punto de vista clínico del siglo 20, juntos con nuestras secciones fijas "redondean" este número.

Aprovecho este espacio para comunicarle a nuestra matrícula que luego de dos años y medio de trabajo duro y sacrificios, el Boletín ha dejado de ser un lastre económico para nuestra Asociación y se ha convertido en una publicación autosuficiente. El hecho de que el Boletín haya evolucionado al punto que no ocasione pérdidas ha permitido a los Directores de nuestra Asociación eliminar la cuota especial adicional establecida hace dos años. La Junta Editora quiere por este medio agradecer a todas aquellas personas que abiertamente manifestaron su apoyo a nuestro órgano oficial, depositaron su confianza en nosotros y juntos debemos compartir la satisfacción del triunfo. Las palabras más apropiadas para esta ocasión podemos recogerlas de un Editorial por el Dr. Ruiz-Arnau en el primer Boletín de la Asociación Médica de Puerto Rico: *"Es la ley del mundo que toda empresa tendente al bien colectivo haya de encontrar en su camino dificultades sin cuento, obstáculos insuperables, antes de alcanzar su completa realización. Pero, por otra ley compensadora, ocurre que a despecho de escollos y valladares llega un momento en que aunándose circunstancias antes improbables y dándose esfuerzos imprevistos, la empresa triunfa, cuando se daba ya por imposible de realizar y cuando aparecía, sarcástica, la sonrisa en los labios de los eternos murmuradores."*

Rafael Villavicencio

Rafael Villavicencio, MD, FACC
Presidente Junta Editora
Boletín Asociación Médica de Puerto Rico

ASOCIACION MEDICA DE PUERTO RICO

BOLETIN



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AGOSTO 1984

NUESTRA PORTADA

"El Entierro de un Chango". Oleo sobre lienzo del artista puertorriqueño Otoniel Morales. El pintor nació en el barrio Maná entre Corozal y Naranjito. Asiste a la escuela Pedro Fernández de Cedro Arriba y luego a la Escuela Superior de Naranjito para terminar en la Escuela Vocacional Superior de Barranquitas. Ingresó a la Escuela de Artes Plásticas del Instituto de Cultura Puertorriqueña obteniendo el grado de Bachiller en Artes Plásticas, entre otros maestros tuvo a Homar, Marín, Alicea, Ríos-Rey y Cervoni.

De profunda raigambre criolla, no obstante su educación formal, sus obras son fieles exponentes de las mejores tradiciones puertorriqueñas.

Sus pinturas de franco tema costumbrista, denotan la presencia de un artista con profundo conocimiento de su trabajo.

Esta y otras obras del pintor se encuentran expuestas en el Taller-Galería André en el Condominio El Centro II de Hato Rey. La Junta Editora agradece al Sr. Andrés Marrero su valiosa colaboración en la consecución de esta obra para nuestra portada.

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- ☐ Prompt, effective relief of bronchospasm
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- ☐ Without the need for blood level testing

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Relief within 30 minutes²...low incidence of tremor

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Especially for children...pleasant cherry flavor, virtually no sugar or alcohol, no tartrazine

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sulfate)

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Syrup
Inhalant Solution

Bronchodilator

Please see following page for brief summary of the prescribing information, including warnings, precautions, and adverse reactions.

**When administered by IPPB

†In repetitive-dosing studies with Alupent Tablets and Alupent MDI, the duration of their effectiveness tended to diminish with time. Present studies are inadequate to explain the divergence in duration of efficacy between single and repetitive dosing.

References:

1. Reilly, EB *et al.* A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. *Curr Ther Res* 1974; 16: No. 8, 759-764.
2. Data on file at Boehringer Ingelheim Ltd.

Alupent[®]

(metaproterenol sulfate)

Bronchodilator

Tablets
Metered Dose Inhaler
Syrup
Inhalant Solution

Alupent[®]
(metaproterenol sulfate)
Bronchodilator

Tablets
Metered Dose Inhaler
Syrup
Inhalant Solution

Contraindications: Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed.

Pregnancy Teratogenic Effects. Pregnancy Category C. Alupent, brand of metaproterenol sulfate, has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose, the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose and 31 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent, brand of metaproterenol sulfate, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents.

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste.

Overdosage: The symptoms of overdosage are those of excessive beta adrenergic stimulation listed under **Adverse Reactions**. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

Adverse Reactions: These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

How Supplied: Round, white, scored tablets of 10 and 20 mg in bottles of 100. Metered Dose Inhaler containing 225 mg of metaproterenol sulfate (300 inhalations); 15 mg per ml (approximately 0.65 mg delivered with each metered dose). Cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 oz bottles. Inhalant Solution 5% in bottles of 10 ml with accompanying calibrated dropper.

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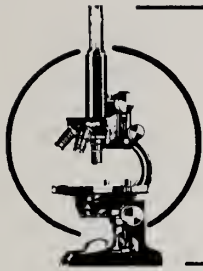
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PATHOLOGY *Review*

María Castillo-Staab, M.D.

Un varón de 58 años de edad, con historial clínico de alcoholismo y cirrosis hepática controlada, fue admitido al hospital con signos de severa decompensación hepática presentando ascites, dolor en el cuadrante superior derecho, ictericia, caquexia y cambios mentales. Las pruebas de laboratorio revelaron una fosfatasa alcalina de 400 UI/L y una alfa fetoproteína de 550ng/ml (normal 20-40 ng/ml).

El escintigrama del hígado reveló defectos de captación en el aspecto inferior del lóbulo derecho. El paciente desarrolló sangramiento masivo del tracto gastrointestinal y falleció seis días después de la admisión.

La autopsia mostró la lesión presente en la Fig. 1



¿Cuál es su diagnóstico?

- a) Adenoma del hígado
- b) Carcinoma de pulmón metastásico al hígado
- c) Síndrome de Budd - Chiari
- d) Carcinoma hepato-celular (hepatoma)
- e) Hamartoma hepático

Carcinoma Hepato-celular (Hepatoma)

El carcinoma hepato-celular es el tumor maligno del hígado que se origina de células hepáticas primitivas diferenciadas hacia células parenquimatosas. Si las células se diferencian hacia conductos y túbulos biliares le llamamos colangio carcinoma.

En Puerto Rico igual que en el resto de América y Europa el hepato-carcinoma es un tumor de baja incidencia que oscila entre 1 a 1.5 por 100,000 habitantes. Es más común en hombres en proporción de 3:1 y en los adultos ocurre asociado con cirrosis u otra forma de daño hepático en un 80% de los casos. Está asociado con hepatitis crónica activa causada por el virus B y menos de un 10% de los casos ocurre en hígados normales. En los niños el hepato-carcinoma, por el contrario, ocurre en hígados normales. Aunque en nuestras latitudes el hepato-carcinoma es un tumor de baja incidencia, existen regiones de África y Oriente donde representa el tumor maligno más común y la incidencia oscila entre 100 y 115 por 100,000 de habitantes. Al presente se postula que la patogenia del hepato-carcinoma está relacionada con la presencia de infecciones persistentes del virus de hepatitis B. Esta relación se ha puesto en evidencia en varios estudios uno de los cuales utiliza de modelo experimental a las marmotas.

Estos animales desarrollan espontáneamente carcinoma de hígado después de episodios de hepatitis persistente debido a un virus similar al de hepatitis B de los humanos.

La presencia de antígenos de superficie (HBsAg) del virus B en el suero de pacientes con hepato-carcinoma varía entre un 50 y un 80%, pero cuando se estudian secciones histológicas de estos tumores utilizando la

técnica de inmunoperoxidasa se demuestra la presencia de antígenos de superficie en un 90% de los casos.

Estudios en Taiwan han demostrado que pacientes con cirrosis alcohólica que al mismo tiempo son portadores del HBsAg desarrollan hepatoma con más frecuencia que los pacientes cirróticos no portadores del antígeno. Se concluye en el estudio que además del efecto tóxico del alcohol se necesita la presencia del virus para iniciar los cambios de malignidad.

En la patogenia del carcinoma hepático también hay que considerar la influencia de otras sustancias hepatotóxicas como son la aflotoxina B₁ y los estrógenos. Se ha encontrado que el uso de contraceptivos orales está asociado con el desarrollo de nódulos hiperplásicos, adenomas y carcinoma del hígado.

Macroscópicamente el hepato-carcinoma suele presentarse en tres formas: masivo, nodular y difuso. El masivo es un tumor solitario, grande que ocupa uno de los lóbulos hepáticos produciendo hepatomegalia marcada. El nodular son varios nódulos tumorales de distintos tamaños a través del hígado y la variante difusa consiste de nódulos pequeños que se confunde con cirrosis. Los tumores son de color blanco amarillentos, con áreas de hemorragias y tienden a invadir los vasos sanguíneos produciendo obstrucción de las venas hepáticas y de la porta.

Microscópicamente (Fig. 2) el hepatocarcinoma es un tumor muy bien diferenciado donde las células malignas se arreglan en cordones muy similares a los hepatocitos normales. Hay variantes anaplásicas con células monstruosas, pero son raras. Las células tumorales conservan muchas de las características funcionales de los hepatocitos y aún en las metástasis forman bilis, lo cual ayuda al patólogo a reconocer su origen hepático.

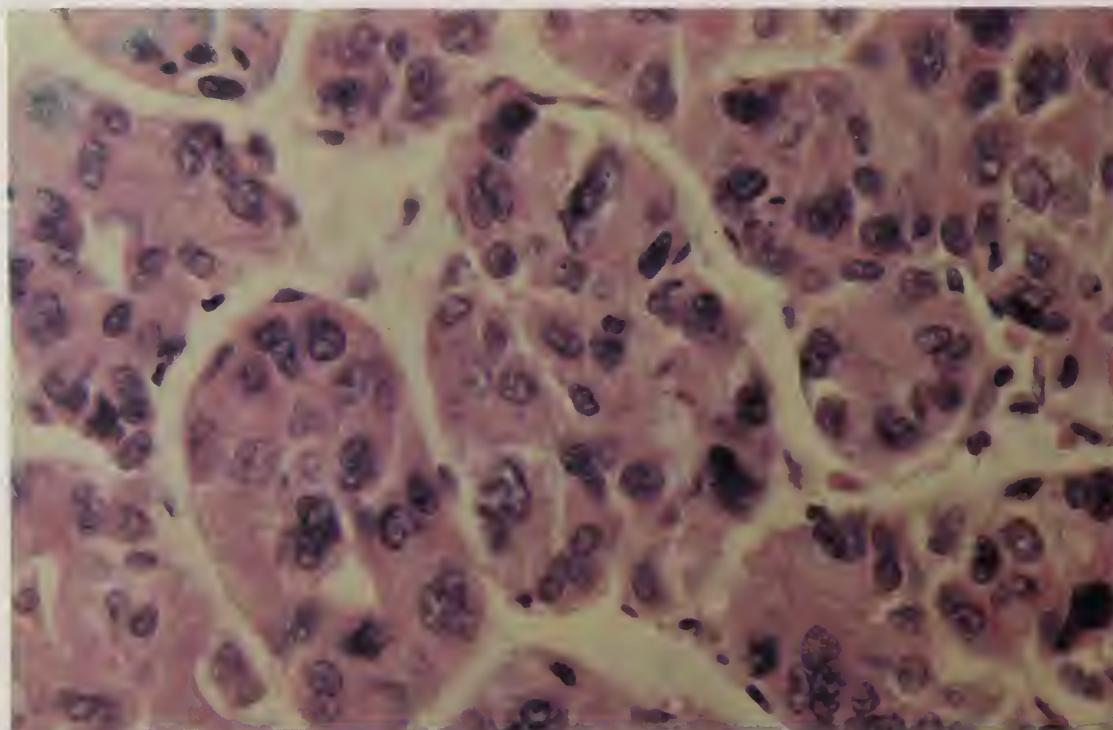


Figura 2. Sección microscópica de un hepatocarcinoma donde pueden apreciarse las células malignas arregladas en cordones.

El carcinoma hepatocelular tiende a permanecer localizado en el hígado por mucho tiempo, pero eventualmente metastatiza a ganglios, pulmón, hueso y adrenales.

Clínicamente el hepatocarcinoma puede presentarse como una hepatomegalia silenciosa pero usualmente aparece en pacientes cirróticos y a veces resulta difícil separar su sintomatología de la del cuadro clínico de cirrosis. Debe sospecharse la presencia de un hepatocarcinoma cuando el paciente cirrótico se decompense rápidamente con acumulación de líquido ascítico (que puede ser hemorrágico), aparezca hepatomegalia, dolor en cuadrante superior derecho, pérdida de peso y fiebre. Desde el punto de vista de estudios de laboratorio la determinación de alfafetoproteína nos ayuda a favorecer este diagnóstico. La alfa fetoproteína es una globulina producida por el hígado fetal la cual alcanza altas concentraciones en el suero fetal en el primer trimestre, desapareciendo casi totalmente después de un año del nacimiento. Las células del hepatocarcinoma producen una proteína similar a la fetal y utilizando el método de radio-inmunoensayo se ha demostrado la presencia de altas concentraciones de la alfafetoproteína en el 90% de los pacientes con hepatocarcinoma. Aunque esta proteína aparece elevada en el suero de pacientes con otras lesiones de necrosis hepática y en pacientes con carcinoma embrionario de testículo, nunca alcanza el nivel observado en los pacientes con hepatocarcinoma. La elevación de la fracción hepática de la fosfatasa alcalina ocurre debido a un fenómeno obstructivo de los canalículos y vías biliares el cual puede ser intra o extra hepático, por lo tanto, pacientes con hepatocarcinoma presentan elevación de la fosfatasa alcalina sérica en concentraciones más altas que la observada en los pacientes cirróticos. La determinación de la fosfatasa alcalina es muy útil también en el seguimiento de pacientes con metástasis hepáticas.

Se pueden utilizar diferentes métodos de diagnóstico cuando sospechamos la presencia de un hepatoma y varían desde el escintigrama hepático con radionucleótidos, angiografía, tomografía computarizada y ultrasonografía.

Para confirmar el diagnóstico se debe realizar una exploración quirúrgica, una biopsia percutánea o una biopsia por peritoneoscopia.

El hepatocarcinoma es un tumor de muy pobre pronóstico no importa cual modalidad de tratamiento se utilice. Aunque algunos casos puedan ser extirpados quirúrgicamente, la sobrevida a cinco años es menor de un 30% incluyendo quimioterapia sistémica, quimioterapia por infusión de la arteria hepática y radiación al área del hígado. Quizás la mejor arma sea la prevención y se postula que el uso de la vacuna contra hepatitis virus B desarrollada últimamente ayude a la prevención de esta lesión en aquellas áreas geográficas donde el desarrollo de hepatocarcinoma parece estar asociado íntimamente con hepatitis persistente debido a hepatitis por virus B.

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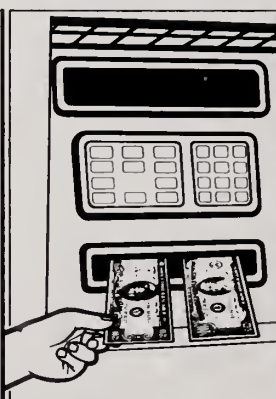
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On cimetidine

Impotent

Childhood
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CNS
problems

Heavy
smoker

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*Patient descriptions are hypothetical composites based
on clinical experience and evaluation of data.*

Rely on one-tablet-a-day for these and virtually

Laura K is depressed... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN[®] (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma.¹ Smoking has been implicated—especially in males.² Cardioselective TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This preference is not absolute.

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence.

Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³

At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.⁴

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen.

Unlike propranolol, cardioselective TENORMIN can reduce the likelihood of bronchospasm in susceptible patients.^{5,6}



dosage and cardioselectivity* all your hypertensives.

*Newly diagnosed...
workup shows
162/100 mmHg. On
cimetidine for pep-
tic ulcer. Don S
hates the thought
of yet another
medication.*

TENORMIN is not
metabolized by the
liver. Its pharmaco-
kinetics are unaf-
fected when it is
administered con-
comitantly with
cimetidine^{7,8} or
ranitidine.⁹

"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

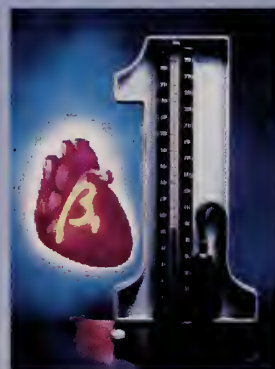
The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹⁰



*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary of prescribing information.



STUART PHARMACEUTICALS



ONE TABLET A DAY TENORMIN® (atenolol)

Therapy
for virtually every
hypertensive
patient in your
practice.



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol: water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages, first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or other anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day, increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min. 1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
< 15	> 27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Electrophysiologic Testing in Patients With Sudden Cardiac Death

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In 1958, Alanis, González and López described His bundle potentials recorded by placing needle electrodes in the atrioventricular groove in the isolated perfused dog heart.¹ Later, Stuckey and Hoffman² recorded the His bundle electrogram in the dog during open-heart surgery. Following this report, Giraud and Peuch³ were the first to record His bundle activity in the human heart during cardiac catheterization in a patient with an atrial septal defect. However, it was not until 1967, that Scherlag described a reproducible technique for recording His bundle potentials in man.⁴

Throughout the past 17 years, significant advances in our understanding of clinical electrophysiology have been made. In this summary the contributions of electrophysiologic testing in determining the presence and defining therapy for patients with atrial and ventricular tachyarrhythmias are made.

Paroxysmal Supraventricular Tachycardia

The most common mechanism of paroxysmal supraventricular tachycardia (PSVT) in humans, is A-V nodal reentry.⁵ The concept of A-V nodal reentry as a mechanism for PSVT was initially proposed by Mines in 1913.⁶ However, it was Moe and associates⁷ who first demonstrated that PSVT could be produced by longitudinal dissociation of the A-V node into two pathways, designated as alpha and beta.

The alpha pathway is slower conducting, but has a shorter refractory period than the faster conducting beta pathway. During sinus rhythm the impulse is conducted through the beta pathway to produce a single ventricular

depolarization. At the same time, the impulse is conducted down the slower alpha pathway to reach the His bundle after it had been depolarized and rendered refractory by the impulse that had been conducted down the beta pathway. If a premature atrial depolarization occurs, the impulse is blocked in the beta pathway (longer refractory period) and conducts slowly down the alpha pathway (shorter refractory period). If conduction down the alpha pathway is slow enough to permit the refractory beta pathway to recover, so that the impulse is conducted in a retrograde fashion to the atrium, an echo beat results.

Electrophysiologic Evidence of Dual Pathway Conduction

Over 75% of patients with A-V nodal reentrant PSVT exhibit dual A-V nodal pathway conduction during atrial stimulation. The dual pathway response to atrial stimulation is identified by a discontinuous response of A-V nodal conduction time to progressively premature atrial premature beats. At longer coupling intervals, conduction occurs down the fast pathway (beta). At shorter coupling intervals, the impulse is blocked in the fast pathway and is conducted down the slow pathway (alpha). This change in conducting pathways from the fast to the slow pathway, is evidenced by an increase of at least 50 msec in the A-H interval when the coupling interval of the premature atrial beat is decreased 10 to 20 msec.

Electrophysiologic studies have demonstrated that tachycardia could be induced in patients with dual atrioventricular nodal pathways whose antegrade slow pathway was capable of rapid repetitive antegrade conduction (as assessed with atrial pacing) and whose retrograde fast pathway was capable of repetitive retrograde conduction (as assessed with ventricular pacing).

Pharmacologic manipulation of the conduction properties (refractory period and conduction time) of these pathways with atropine can facilitate induction and maintenance of PSVT. On the other hand, depressing retrograde fast pathway conduction with procainamide may prevent induction of PSVT.

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Reverse Circuit Tachycardia

An unusual type of A-V nodal reentry was reported by Wu et al⁹ in 1977. In the reverse circuit tachycardia, the fast pathway is used for antegrade conduction and the slow pathway for retrograde conduction. When this occurs, the P wave during the tachycardia precedes the QRS complex with a short PR interval. This pattern is only seen in 5 to 10% of patients with A-V nodal reentry and is characteristic of an incessant form of A-V nodal reentrance tachycardia.

Retrograde Atrial Depolarization Sequence During Paroxysmal A-V Nodal Reentrant Tachycardia

During retrograde atrial depolarization, the earliest site of atrial activity is recorded in the His bundle electrogram and corresponds to the low septal right atrial area closest to the A-V node. The atrial activity corresponding to the left atrium as recorded from the proximal third of the coronary sinus follows, and precedes the atrial electrogram from the high right atrium. The atrial electrogram recorded from the distal coronary sinus occurs just before the high atrial depolarization, however, on occasions it may occur simultaneously or follow the high right atrial electrogram by about 5 msec.

Pre-excitation Syndromes

The three most common supraventricular arrhythmias seen in patients with atrio-ventricular pre-excitation (WPW) can be summarized as follows:

1) *Narrow QRS tachycardia* characterized by antegrade A-V nodal conduction and retrograde conduction through the A-V pathway.

In a recent study, Denes et al¹⁰ assessed the significance of the induction of narrow QRS reentrant tachycardia in patients with WPW. The authors reported that the tachycardia was inducible in the laboratory in all patients with documented PSVT, in 67% of patients with documented atrial fibrillation, in 36% of patients with palpitations without documented arrhythmias and 8% of asymptomatic patients with pre-excitation. The authors concluded that laboratory induction of narrow QRS reentrant tachycardia was a clinically significant event that was directly related to the ability to have spontaneous paroxysmal supraventricular tachycardia.

2) *Wide QRS tachycardias* - these are less frequent and may be secondary to the following mechanisms:

- a) bundle branch block during A-V reentrance
- b) atrial flutter with 1:1 conduction over the A-V accessory tract
- c) A-V nodal reentry with antegrade conduction over the anomalous pathway and retrograde conduction through the A-V node.
- d) reentrant tachycardia utilizing two or more anomalous pathways.

3) *Atrial fibrillation* - ventricular fibrillation in patients with WPW syndrome is usually caused by atrial fibrillation with rapid ventricular response due to a short (200 msec) refractory period of the anomalous accessory pathway. The shortest R-R interval during atrial fibril-

lation in a patient with WPW defines the refractory period of the accessory pathway. Electrophysiologic testing with electrical induction of atrial fibrillation is helpful in identifying high risk patients for the development of ventricular fibrillation.

Concealed Atrio-ventricular By Pass Tracts

In about 20-30% of patients with paroxysmal supraventricular tachycardias, the mechanism of reentry consists of antegrade conduction through the A-V node and retrograde conduction through an accessory A-V by pass tract.¹¹

The electrocardiogram during sinus rhythm in these patients does not reveal pre-excitation. In our experience, most of the patients with concealed pre-excitation have had left sided by pass tract although right sided concealed accessory pathways have been documented.¹¹ The most helpful electrocardiographic finding during supraventricular tachycardia in which the reentrant circuit utilizes a concealed accessory pathway is an inverted P wave after the QRS complex with a V-A or V-P interval greater than 95 msec. The decrease in the R-R interval of the tachycardia when functional bundle branch block (BBB) appears, indicates an accessory by pass tract ipsilateral to the BBB.

Therapy and Electrophysiologic Testing

Several groups of investigators have independently reported¹²⁻¹⁴ that acute electrophysiological responses to intravenous agents predicted the electrophysiological responses to oral agents. More important, these studies suggested that electrophysiological responses to intravenous and then oral drugs predicted subsequent clinical course. Short term follow up of these patients demonstrated major clinical improvement with resultant suppression of recurrent episodes of supraventricular tachycardia. Although in these patients, similar therapeutic regimes could have been made out of trial and error, the chronic electrophysiological study allowed a rapid delineation of a successful oral drug regime.

Contributions of Electrophysiologic Testing to our Understanding of Ventricular Tachycardia

Wellens et al¹⁵ were the first to describe the use of programmed stimulation techniques in the evaluation of ventricular tachycardia. From this and other studies, it appears that the electrophysiologic requirements needed to initiate and terminate ventricular arrhythmias are very similar to those required for supraventricular tachycardias. However, although the site of the reentrant pathway has been determined in most of the cases of supraventricular tachycardias, this has not been the case in ventricular tachycardias.

At the present time, most patients are referred for electrophysiologic testing when previous drug therapy has failed. In addition, patients with sporadic ventricular arrhythmias of major hemodynamic significance or with one episode of prior rescued sudden death should be referred for electrophysiologic study irrespective of the results of previous drug therapy. An arbitrary classification proposed by Denes⁸ is as follows:

- 1) *Chronic recurrent sustained ventricular tachycardia*

This rhythm disturbance lasts one minute or more, may convert spontaneously or require pharmacologic and electrical cardioversion. It may also degenerate into ventricular fibrillation. Recurrent sustained ventricular tachycardia associated with chronic coronary artery disease is usually reentrant and can be induced with programmed ventricular stimulation in 90% of patients with documented spontaneous sustained ventricular tachycardia. Induction can be readily accomplished with double extrastimuli from the RV in 90% of the cases. The factors most frequently associated with successful medical treatment are: age (<45 years), ejection fraction greater than 50%, hypokinesia as the only contraction abnormality and the absence of organic heart disease. Four other findings have been correlated with medical treatment failure: induction of ventricular tachycardia with a single ventricular extrastimuli, an HV interval greater than 60 msec, the presence of a left ventricular aneurysm and Q waves in the baseline electrocardiogram.¹⁷

2) *Non-Sustained Ventricular Tachycardia* - This has been arbitrarily defined as ventricular tachycardia, ranging from 5 beats to 1 minute in duration, which spontaneously converts to sinus rhythm. This form of rhythm disturbance in the absence of ischemic heart disease, is extremely difficult to reproduce during electrophysiological evaluation. However, it is considered an independent risk factor for sudden death in patients with coronary artery disease who have sustained an acute myocardial infarction.^{8, 18}

Denes et al⁸ and Rahilly et al¹⁹ have recently described a group of patients with repetitive non-sustained ventricular tachycardias who have relatively good prognosis. These patients are mostly women without demonstrable heart disease. However, in some of the patients, mitral valve prolapse and congestive cardiomyopathy were diagnosed.

3) *Ventricular Fibrillation Related to Sudden Death* - In patients who have survived an episode of out-of-hospital cardiac arrest, about 70% have been reported to have inducible ventricular tachycardia with programmed ventricular stimulation.^{11, 19} The high incidence of inducible ventricular tachycardia instead of ventricular fibrillation in this group of patients, suggests that ventricular tachycardia associated with hemodynamic deterioration is the most frequent precipitating cause of ventricular fibrillation and sudden cardiac death.⁸ Induction of ventricular fibrillation in survivors of cardiac arrest, identifies a subgroup of patients with high risk for future occurrence of this rhythm disturbance.

Morady and co-workers¹⁶ in their study of 45 patients who survived cardiac arrest, reported that ischemic heart disease was the underlying disease in 80% of the patients studied. Congestive cardiomyopathy, valvular disease, mitral valve prolapse and IHSS were entities identified in 20% of their population.

Invasive Testing for Substratification and Risk Determination in Patients with Ventricular Arrhythmias

Programmed electrical stimulation of the heart has been proposed as a technique that can identify patients at

high risk for future cardiac events.²⁰ Greene et al was the first to report the value of the repetitive ventricular response (RVR) to electrical cardiac stimulation in determining the appearance of subsequent ventricular arrhythmias in survivors of acute myocardial infarction.²⁰ He defined the RVR as the occurrence of 1 to 4 ventricular complexes after an electrically induced ventricular depolarization during normal sinus rhythm, atrial or ventricular pacing. Of 48 patients studied, 17 patients (35%) manifested RVR after a single ventricular paced beat during atrial pacing. The interesting finding was that during a one year follow-up, 15 of the 17 patients with RVR developed ventricular tachyarrhythmias or sudden death as compared to 4 of 29 patients without RVR. Subsequent studies reported by Livelli et al,²¹ Ruskin et al,²² and Vandepol et al,²³ did not support Greene's observations. They demonstrated that RVR was not a frequent finding induced by one ventricular extrastimuli during sinus rhythm or atrial pacing and that the relationship of RVR and sudden death was not as useful as reported by Greene. They concluded that RVR had a low sensitivity and specificity when induced as described; a single electrical ventricular extrastimuli during atrial pacing (A₁ V₂ technique).

Livelli and co-workers²¹ also used a different and more aggressive pacing protocol in patients with clinically documented ventricular tachycardia and ventricular fibrillation. They introduced one or two electrical extrastimuli during ventricular pacing (V₁ V₂ or V₁ V₂ V₃ technique). With this approach, the sensitivity of the RVR (ability to identify the true positive) increased to 92%, however the specificity (ability to identify the true negative; patients without ventricular tachyarrhythmias) was low (57%) and had a false positive rate of 43%.

Vandepol²³ and Ruskin²⁴ also demonstrated that even if the RVR was sensitive but not specific, the initiation of sustained or non sustained ventricular tachycardias or ventricular fibrillation identified patients with the clinical occurrence of these rhythm disturbances. In a group of 527 patients Vandepol showed that sustained ventricular tachycardia (SVT) was induced by cardiac stimulation in 95% of patients who had clinical spontaneous documented SVT before the study. Non sustained ventricular tachycardia (NSVT) was induced in 62% of patients who had the tachycardia clinically. In patients resuscitated from out-of-hospital cardiac arrest, ventricular arrhythmias were inducible with the V₁ V₂ V₃ technique, right

TABLE I

Sensitivity and Specificity of RVR, SVT, NSVT and VF in Identifying Patients with Recurrent Ventricular Tachyarrhythmias

RESPONSE	P E S	SENSITIVITY	SPECIFICITY
RVR	A ₁ V ₂	15-30%	50%
RVR	V ₁ V ₂ or V ₁ V ₂ V ₃	92%	57%
SVT	V ₁ V ₂ or V ₁ V ₂ V ₃	95%	98%
NSVT	V ₁ V ₂ or V ₁ V ₂ V ₃	62%	95%
VF	V ₁ V ₂ or V ₁ V ₂ V ₃	75%	95%

PES: programmed electrical stimulation

RVR: repetitive ventricular response

SVT: sustained ventricular tachycardia

NSVT: non sustained ventricular tachycardia

VF: ventricular fibrillation

or left rapid ventricular pacing before and after infusion of isoproterenol in 65 to 85% of patients studied. In patients without clinically documented sustained ventricular tachycardia (SVT) it can be induced in about 1-2% of them.

Programmed electrical stimulation of the heart has a sensitivity of 95% and a specificity of 98% in identifying patients with recurrent sustained ventricular arrhythmias.

After identification of the patient that has had clinical recurrent malignant ventricular tachyarrhythmias, the next logical approach is to institute effective drug therapy to prevent recurrences of the rhythm disturbance. The most effective method to define efficacy of therapy is at present controversial. One approach is based on electrophysiologic testing to assess the efficacy of drug therapy by their ability to prevent the initiation of ventricular tachyarrhythmias by programmed electrical stimulation. The other method employs suppression of spontaneous ventricular arrhythmias as documented by ambulatory electrocardiographic monitoring and treadmill exercise tests.

Non Invasive Studies and Evaluation of Drug Therapy

Graboyes et al²⁵ recently reported their findings using non invasive tests to evaluate suppression of ventricular arrhythmia. They studied 123 patients with a history of documented ventricular tachycardia or ventricular fibrillation and defined drug efficacy as the elimination of repetitive forms of ventricular depolarizations and R on T phenomena (4A, 4B and 5 of Lown classification).

The annual mortality rate in the 98 patients in whom the drug efficacy was achieved was 2%, as compared to a 44% of mortality in the group in whom drug efficacy was not achieved. Although their study was uncontrolled and retrospective, it is of extreme importance since it showed that control of high grade and complex forms of ventricular arrhythmias reduces mortality in patients with documented ventricular tachycardia or fibrillation. It should also be stated that the methodology employed by Graboyes et al, included an 8-12 days hospitalization, 10-12, 24 hours ambulatory electrocardiographic monitoring per patient, 10-12 exercise tests per patient and multiple serum drug determination. Obviously the availability of these procedures, costs involved and personnel needed to study large groups of patients should be considered.

Further work is required before this approach can be generally employed. The precise protocol and criteria used to define drug efficacy are not clearly defined and could benefit from standardization. In addition, the therapeutic approach to the patient with paroxysmal ventricular tachyarrhythmia who does not have frequent and complex ventricular arrhythmia during ambulatory monitoring remains unclear in this protocol, although Graboyes and co-workers found few such patients. Finally, these studies were performed in patients with a previously documented episode of hemodynamically significant ventricular tachycardia or ventricular fibrillation where the risk of recurrence is known to be high. Whether these results will be replicated in patients with chronic high grade ventricular arrhythmias, especially

after acute myocardial infarction, where the overall risk of sudden death is less, is unknown.

Electrophysiologic testing has been applied very effectively to the prospective selection of antiarrhythmic regimens of patients with recurrent ventricular tachyarrhythmias and for patients resuscitated from out-of-hospital cardiac arrest.^{26, 27} Therapy is based on suppression of inducibility of the tachyarrhythmia by antiarrhythmic drugs. In many (60% to 80%) survivors of out-of-hospital cardiac arrest, programmed stimulation can induce ventricular tachyarrhythmias and thus electrophysiologic testing can be used to assess efficacy of drug regimens. Ruskin et al reported their experience in treating 31 such patients using the electrophysiologic technique.²⁴ In 19 of 25 patients in whom arrhythmias were inducible, drug therapy suppressed the inducible arrhythmia in a follow-up period of more than 1 year. In those patients in whom the arrhythmia could not be suppressed, the mortality rate from sudden death was 50%. Similar results have been reported by others.²⁷

Limitations of Electrophysiologic Testing

Testing techniques vary considerably among electrophysiologic laboratories, and these differences frequently interfere with analysis of data from different centers. The results of ventricular stimulation depend in large part on such technical factors as the site of stimulation, the number of extrastimuli, the rate of pacing during extrastimulation and the current strength and duration of the stimuli. These factors must be assessed before the sensitivity, specificity and results of any individual study are compared with those of other studies. Increased sensitivity can be achieved by performing left ventricular stimulation; however, additional risks are incurred with the use of arterial catheterization. Similarly, sensitivity can be increased by using triple extrastimuli or high stimulating current strength, or both; however, the effects on specificity have yet to be determined.

Invasive electrophysiologic studies, even if accurate in identifying patients at risk of sudden death, have certain disadvantages. They are relatively time consuming and require specialized equipment and personnel. The risk of electrophysiologic catheterization as well as the morbidity and potential mortality associated with programmed stimulation and induction of hemodynamically significant ventricular tachyarrhythmias in a patient recovering from a recent myocardial infarction must be taken into account. Although these factors must be considered, if these procedures are performed by adequately trained personnel in appropriate settings the risks and potential morbidity should be low and acceptable.

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Fotografía de un mapa del siglo 18, donde se detallan los puertos y bahías de Aguada, Añasco y Mayagüez y en la otra parte el puerto de Arecibo.

Estos puertos y bahías fueron estudiados y sondeados por orden del gobernador de la época, determinados como "seguros y adecuados" para

proveer de agua a la flota española en su camino a Méjico.

Tomada del Archivo General de Indias (Sevilla), Sección de Mapas y Planos, Audiencia de Santo Domingo. Expediente 198, Legajo 2499.

Fotografía cortesía del Dr. José G. Rigau



Foro de Medicina Nuclear

Scintigraphic Localization of Lower Gastrointestinal Bleeding

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Julio V. Rivera, M.D.
Oscar Arill, M.D.

Case Summary

A 64 year old male with history of end stage renal disease on hemodialysis, atherosclerotic heart disease with angina pectoris and arthritis, was admitted to the hospital on March 24, 1984 due to an episode of tarry stools accompanied by diffuse abdominal pain. At the time of admission he presented with right flank pain upon palpation, without abdominal guarding or rebound tenderness. Rectal examination showed no evidence of intenal or external bleeding hemorrhoids; but a stool sample taken at this time showed a strongly positive guaiac test (+++). Nasogastric tube lavage was clear and the hematocrit was 30% (at Emergency Room). The same day of admission, this patients needed two units of packed red blood cells after the hematocrit decreased to 27%.

On March 26, 1984, the patient passed bright red blood per rectum and his blood pressure dropped to 60/30mm Hg. The hematocrit was found to be 23%. Sigmoidoscopy revealed port-wine diarrhea coming from more than 15cm above the anus. Gastrosocopy showed normal gastric and duodenal mucosa. Definite lower gastrointestinal bleeding was postulated clinically at this time.

Since persistent rectal bleeding continued a 99m Technetium-labeled red blood cell abdominal scan was performed on March 28, 1984. This study demonstrated focal activity in the upper right colon during the venous phase. Serial images showed movement of this pooled activity from the right colon across the transverse colon, demonstrating active bleeding in the ascending portion of the right colon with distal intraluminal blood transit.

A right hemicolectomy on March 29, 1984 found diverticulosis with diverticulitis and intestinal bleeding from erosion of terminal arteries and submucosal vessels in the ascending colon.

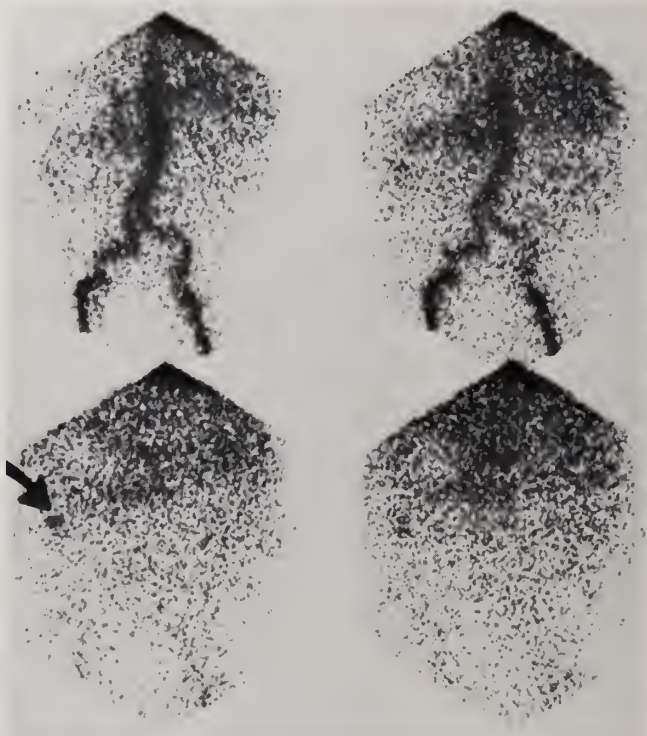


Figure 1. Rapid sequence scintiphotos of the abdomen (99mTc-RBC) March 28, 1984 reveal in the initial phase focal pooling of activity in the right side of the abdomen (arrow).

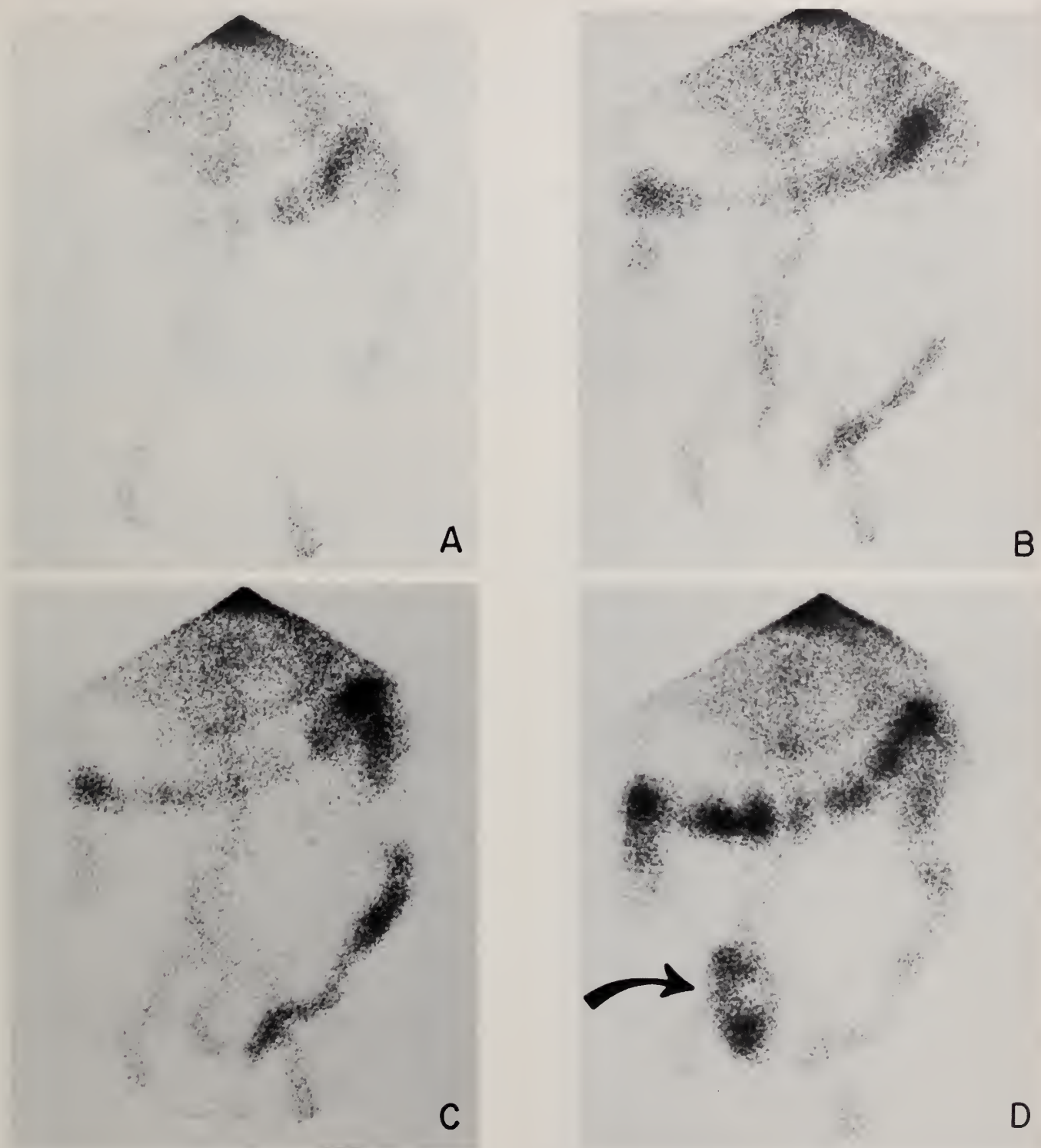


Figure 2. Scintiphotos at 8 minutes (A) show activity in mid-ascending and transverse colon; at 20 minutes (B) and 31 minutes (C) increased activity in same distribution. At 60 minutes (D) images, activity projecting over inferior abdomen (arrow) was actually bloody stools on the bed.

Discussion

Lower gastrointestinal bleeding is a serious and potentially lethal complication of multiple abdominal pathologic processes, like colonic diverticula, angio-

dysplasia, inflammatory bowel disease and eroding gastrointestinal neoplasia.^{1, 2} Lower gastrointestinal bleeding is usually indicated by the presence of melena,

hematochezia, orthostatic hypotension and anemia. The sites of bleeding are usually identified by abdominal angiography or endoscopy. Fiberoptic endoscopy has not been employed successfully in evaluation of acute colonic bleeding above recto-sigmoid level due to the difficulty in preparing the colon for an adequate examination in these patients.

Abdominal angiography can accurately identify and locate the sites of lower gastrointestinal bleeding, but the procedure complications increase in proportion to the intravascular contrast load injected and the duration of the whole study if the three gastrointestinal arterial trunks are to be evaluated. Also, for detection of bleeding the angiogram should coincide with episodes of active bleeding greater than 0.5 ml/min.³ Since this bleeding is usually intermittent or episodic, a patient not actively bleeding at that instant may go undiagnosed angiographically even though he starts bleeding again after the procedure.

Technetium 99m-labeled red blood cells (99mTc-RBC) are being used to evaluate patients suspected of having gastrointestinal bleeding.⁴ This radionuclide preparation remains in the circulation for a prolonged period of time allowing serial imaging up to 24 hours post injection. Since the blood pool remains "marked" during such a long time, intermittent or small bleeding occurring during this period will produce radionuclide extravasation detectable in serial imaging.

Experimental evidence indicates that bleeding as small as 0.05 ml/min may be detected.⁵ This allows us to locate the bleeding source and the vascular distribution from which the bleeding is originating.

Winzelberg, et al,⁶ accurately located the site of hemorrhage in 83% of patients in a prospective study of 100 patients with gastrointestinal bleeding. The study is more accurate if areas of extravasation are detected on early images (first 15 minutes). If the abnormal 99mTc-RBC accumulation is first noticed on delayed images (later than one hour) the activity may be related to bleeding at that site or from a proximal location. The findings of increased radionuclide intensity and distal bowel movement of extravasated 99mTc-RBC on serial imaging are criteria for active bleeding.

99mTc-RBC studies for evaluating gastrointestinal bleeding are particularly helpful in elderly patients with underlying medical problems such as renal failure, diabetes, heart failure or peripheral vascular disease, in whom emergency angiography entails increased risks. If angiography is needed at all, it will be directed towards the site where bleeding was documented by the 99mTc-RBC study, decreasing the study duration and contrast load and with this, minimizing angiography's inherent risks. A negative 99mTc-RBC study in these patients with suspected bleeding is good evidence that angiography would not detect the site of hemorrhage at that moment. In this way emergency angiography could be deferred, and elective angiography or fiberoptic endoscopy could be performed after the patient is adequately prepared and stabilized.

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LISTA DE ANUNCIANTES

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Presentación de Casos

Dissecting Aneurysm of the Aorta: an Unusual Complication of Mitral Valve Prolapse

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José Martínez, M.D.
Héctor Banchs, M.D.

Abstract: A 33 year old female patient with an atrial septal defect and prolapse of the mitral valve had a dissecting aneurysm of the aorta. The probable interrelation between dissecting aneurysm and prolapse of the mitral valve is discussed.

Case Summary

V.R. was a 33 year female patient with an atrial septal defect and a prolapse of the mitral valve without mitral insufficiency, proven by cardiac catheterization. Surgery was recommended, but she refused. She did well until a week prior to this admission, when she had a dizzy spell. She was seen in a community hospital where she was found hypotensive, with a hematocrit of 29% and a wide mediastinum by chest X-ray. An electrocardiogram showed a right intraventricular conduction defect and no arrhythmias. She was referred to the University Hospital where she was evaluated and a dissecting aneurysm was suspected. An aortogram (Fig. 1) showed a dilated aortic root with dilation of the origin of the innominate and left subclavian arteries, and a type III aortic dissection starting distal to the origin of the left subclavian artery up to the aortic bifurcation. An injection in the false lumen was done. Surgery was considered on an emergency basis, but she had a cardio-respiratory arrest and died. No arrhythmias were detected. We assumed that the cause of this catastrophe was rupture of the aneurysm. Necropsy was not done.

Figure 1



Discussion

Mitral valve prolapse is a spectrum in all aspects of its clinical presentation. Usually mitral valve prolapse is classified as primary (idiopathic) or secondary, when it is related to another heart disease. Usually most of the reported complications of the syndrome have been reported in the idiopathic syndrome and not in the secondary.

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The left ventricle of patients with atrial septal defect usually is a small ventricle with or without mitral valve prolapse. Around 20% of atrial septal defects will show the angiographic appearance of mitral valve prolapse. The degree of prolapse varies from minimal to a full appearance of prolapse. Rarely, mitral insufficiency is seen. The importance of this prolapse in atrial septal defect is not clear. Several investigators¹ think that this angiographic picture is produced by the shunt and there is no relation with the idiopathic type. At present this is not clear. We think that when the prolapse is big it may represent a true idiopathic prolapse which may be accompanied by all the complications of the idiopathic prolapse.

Some of the complications seen in patients with prolapse of the mitral valve are 1. arrhythmias 2. rupture of the chordae tendinae with severe mitral insufficiency, 3. systemic embolism and 4. endocarditis.

That we know, there has not been a report of a dissecting aneurysm related to this entity. Some investigators have described myxomatous transformation of the aorta in some patients with mitral valve prolapse, but of the idiopathic type. Read² relates myxomatous transformation of the mitral valve to a form fruste of Marfan's syndrome. This patient didn't have the characteristics of a full Marfan's syndrome, but she was a thin, tall women and the possibility of a form fruste was thought. Also Brown and associates³ found an echocardiographic mitral valve prolapse prevalence of 91% and a murmur of mitral regurgitation and or systolic clicks in 46% of 35 patients with Marfan's syndrome. This points to the relation of mitral valve prolapse and Marfan's syndrome and its complications. It is accepted that dissecting aneurysm is a common complication of Marfan's syndrome. In our experience almost all Marfan's syndromes catheterized in our laboratory due to severe aortic insufficiency will show mitral valve prolapse in the ventriculogram.

Presently it is not clear if the pattern of mitral valve prolapse seen in some ventriculograms of patients with atrial septal defect represents a true prolapse or is produced by the shunt or by the abnormal geometry of the left ventricle. The only problem our patient had was the shunt, and there was no doubt about the dissection, because it was proven by angiography. Due to this correlation seen in this patient with a big angiographic mitral valve prolapse appearance and a dissecting aneurysm, it is our opinion that dissecting aneurysm should be added as a rare complication of mitral valve prolapse.

Resumen: Una mujer de 33 años con un defecto interatrial y prolapso de la válvula mitral tuvo una disección de la aorta. La probable relación entre disección de la aorta y prolapso de la válvula es discutida.

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SIRVIENDO AL PUEBLO Y A LA PROFESION MEDICA



ASOCIACION MEDICA DE PUERTO RICO



MEDICAL ASPECTS OF NUTRITION

Fad Reducing Diets: Separating Fads From Facts*

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It has been estimated that between 15%-40% of the U.S. population can be classified as obese, a national, nutritional problem that has been expanding to epidemic proportions rather than diminishing in recent years. Today, more than 80 million Americans are considered overweight and 40 million are clinically obese.

That our population is increasingly getting heavier is demonstrated by the 1977 survey which revealed that non-obese adults under the age of 45 and of the same height were 4 pounds heavier than their counterparts in 1961.

Mortality statistics, on the other hand, show a 12-fold increase in the death rate among grossly obese men between 25 and 34 years of age, about 6-fold increase for the 35- to 44-year age group, and a 3-fold increase for ages 45 to 54 years.¹ This excess mortality noticed in obese individuals is believed to be caused primarily by increased rates of deaths from coronary heart disease, strokes and diabetes mellitus—diseases linked with obesity.²

Obesity-related medical disorders have triggered an explosion in the treatment of obesity. Weight loss is not, in itself, a cure for obesity. The failure of the currently available programs to treat the disease is highlighted by the very small rate of success. Less than 5% of those who have lost the extra weight have maintained it for more than a year.³ This failure has brought about the proliferation of fad diets and has created a widespread multibillion-dollar business.

Americans brought up in a society full of technological miracles are constantly searching for the easy way out. In desperation, they are willing to try anything offered to them, wasting money, time and sometimes their own lives.

Total Fasting

Total fasting as a means of treating obesity was first introduced in 1954.⁴ Fasting subjects exhibit an anorexic behavior, characterized by a progressive reduction in intestinal activity during the fasting period, altering the overall physiological and biochemical activities of the gastrointestinal tract.⁵

Total starvation, because of the hazards associated with it, should be under complete medical care. Potassium, sodium, bicarbonate and multivitamin-mineral preparations must be supplemented.⁶

Various complications associated with total starvation include:

- dehydration
- increased uric acid levels
- nausea and dizziness
- hepatic and renal impairment
- mineral loss
- acidosis
- hyperuricemia
- severe postural hypotension
- muscle wasting

Protein loss, as indicated by a severe negative nitrogen balance, can be very high (from 3-5 grams per day). It has been estimated that one third of the weight lost during a 24-day fast is fluid and lean body mass.⁷ It is not surprising that this weight is quickly regained.

Drug/Hormone-Induced Weight Loss

As the conventional methods of weight management fail to deliver promised results, more and more Americans are turning to what they consider *the easy solution*—pill popping and injections. A survey of over 200 controlled studies performed by the Food and Drug Administration on the efficacy of anorectic agents concluded that the administration of these agents resulted in a loss of only about 0.23 kilogram of weight per week during a 24-week period. Most individual efforts last for 6 weeks.

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Most of the appetite suppressants are derivatives of the amphetamine molecule. In addition, diethylpropion, maxindol, thyroid hormone and many others are commonly in use. All of these drugs have a different mode of action; however, they commonly increase thermogenesis or depress the appetite.

Thyroid Hormones

It is a mistake to believe that all obese individuals are hypothyroid or suffer from a malfunctioning thyroid gland. The fact is that fewer than 1% of overweight patients exhibit abnormal thyroid function. Administration of thyroid hormones is associated with reduced body weight, but it will not restore normal thyroid gland functions.⁸

The medical complications are worth mentioning. Its administration causes palpitations, sweating, increased heart rate and systolic blood pressure. In addition, urine calcium excretion is increased, which may potentiate the development of osteoporosis.

Weight loss is primarily muscle mass (80%-90%); therefore, if fat loss is the goal, thyroid hormones do not appear to be useful and safe agents.⁹

Growth Hormone and Human Chorionic Gonadotrophin

Growth hormone mobilizes fatty acids while preserving muscle mass and increasing oxygen consumption in obese individuals.¹⁰ Although it seems to be a hormone that affects weight loss, its use is restricted due to limited availability.

Injections of human chorionic gonadotrophin (HCG) hormone obtained from the urine of pregnant women has been suggested in the treatment of obesity.¹¹ Its mechanism has not been established. Advocates of HCG treatment have proposed several features, including reduction of hunger symptoms, production of euphoria and a redistribution of fat.

Recent studies indicate the effects of HCG on lipolysis are induced indirectly through thyroid stimulation. The American Medical Association warns against its use. It has no benefit to a very low-calorie diet beyond that of a placebo.

Very Low-Calorie Diet

Liquid supplemented, very low-calorie diets are now being widely used. They come in powder form and are mixed with water, club soda, any noncaloric beverage or with fruit juice. They are usually a mixture of protein, carbohydrates and minimal fat. Their very low-caloric content (from 300 to 800 kcals) has raised many questions about their safety and nutrient adequacy. Despite promotional claims, muscle mass is not preserved with such diets. Serious, sometimes fatal, complications have been attributed to these diets.^{12, 13} One of them, the liquid protein diet, is reported to have caused a number of deaths. It is free of most micronutrients and consists of hydrolyzed collagen or gelatin derived from animal hide, tendons, bone, and other by-products of the meat industry.

The "Cambridge Diet" is the most widely used liquid formula sold directly to the public. It is composed of 44 grams of carbohydrate, 33 grams of protein and 3 grams of fat, for a total of 330 kcals. Minerals and vitamins have been added to meet the recommended daily allowances (RDA). The RDA, however, were established for individuals under usual environmental stresses and not while under severe caloric restriction.

Overall, very low-calorie diets are characterized by ketone excretion through the urine. This phenomenon has led to nonscientific conclusions among the public that when the body goes into ketosis, fat is broken down into ketones and excreted as unused calories in the urine. The truth of the matter is that the caloric value of these excreted ketones very rarely exceeds 100 kcal per day and its contribution to weight loss is negligible. Long-term weight loss in such diets is due to caloric restriction alone.

The greater weight losses noticed on the very low-calorie diets, when compared to the balanced diets of equal caloric content, are attributed solely to the large amount of water loss, which is regained as soon as the diet is terminated.¹⁴

Choice Elimination Approach

There are those who believe that the best approach to weight loss is the restriction not only of calories but of food choices as well. These diets emphasize elimination of whole groups of foods or inclusion of only a few foods. This approach is the product of our society's false notion that fast and easy methods will work; therefore, the fewer food choices the dieter has to make, the better and faster the results will be.

Promoters of fad diets use catchy names, such as "The Amazing Diet Secrets of a Desperate Housewife," or others claim "Reducing the quantity of calories is generally not necessary to lose weight." Such statements have been made by self-acclaimed, weight-control experts, resulting only in one more disappointment for the dieters. Claims based on nonscientific evidence are made from time to time. Some experts will promote the "eat as much protein and fat as you want, but no carbohydrates, and you will lose weight."

The misleading lecithin, vinegar, kelp, B₆, candy and lollipop diets do not make sense from a metabolic point of view and the claims of their promoters are outrageous. Others go to the extreme of adopting the philosophy of the Zen microbiotic diet. Based on the theory that you can train your body to survive only on brown rice and tea, the Zen diet eliminates foods step-by-step. No stage of this diet, however, provides the needed nutrients to sustain life, and it is possible to become anemic, develop scurvy and even cause death if one stays on the diet for a prolonged period of time. Still other fad diets claim to contain certain enzymes that stimulate the breakdown of fat. However, all lack scientific backing.

All low-calorie diets should be used only under medical supervision. They are especially dangerous for people who have kidney problems or cardiovascular complaints. Low-calorie diets are deficient in vitamins and minerals, some more than others. Daily supplements are necessary.

There are many *ifs* that all prospective dieters should be aware of in judging various diet programs. **AVOID THESE DIETS IF IT...**

- promises fast and easy solutions to your weight problem. There is no simple and easy solution.
- promises to help you achieve ideal weight without mental inspiration and perspiration. Do not believe them. All accomplishments in life need both inspiration and perspiration.
- favors one food as the answer to weight problems. Avoid them. They are either ignorant of the basic daily metabolic needs of the body or they capitalized on your overwhelming desire to lose weight. They are dangerous to both your health and wealth.
- promised to reveal to you the "secret formula" that was developed in some unknown laboratory; we can guarantee that it was done in their effort to make money. Stay away from them. They do not deserve your attention.
- promises you that your fat will "melt away" without a lot of boring, strenuous, grueling exercise and without giving up all the foods you really love, no rigid diet, no hunger pains, no leaving the table still craving a bit more. Do not let them insult your intelligence. Turn your back and go on.

A Good Diet

A logical weight-reduction program should include:

- A nutritionally balanced caloric intake from all major food groups.
- A reasonable increase in physical activity.
- An understanding of behavior modification methods accompanied by cue control techniques and practical experience of relaxation training.

Summary: Generally, it is wise to stay away from any crash diet. All tend to be nutritionally unbalanced. Although all may cause great temporary weight losses in short periods of time, over the long term, the only thing they accomplish is the addition of another cycle of frustration and disappointment for the dieter.

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Nutrition in Cystic Fibrosis*

Philip M. Farrell, M.D., Ph.D.**

Cystic fibrosis (CF) is a congenital metabolic disease characterized by excessively viscous exocrine gland secretions which may obstruct pancreatic and bile ducts, intestine and bronchi.¹ Although about 15% of such patients are spared from the pancreatic lesion, usually pancreatic insufficiency, gastrointestinal malabsorption and frequent pulmonary infections predispose individuals with cystic fibrosis to malnutrition.

Factors Influencing Malnutrition

Nutritional deficiencies in cystic fibrosis are most likely to occur in the first few years of life when natural growth rates and nutritional demands are at their peaks.² However, many variables influence the nutritional status of CF patients so that nutritional deficiencies may occur at any time and with varying degrees of severity, depending upon:

- 1) The degree of steatorrhea (excessive excretion of fat through the bowel).
- 2) The degree of azotorrhea (excessive excretion of protein through the bowel).
- 3) Intestinal resection necessitated by bowel obstruction, reducing absorptive capabilities further; this is usually due to meconium ileus in the neonatal period.
- 4) Growth rate, which increases relative nutritional requirements when weight gains are high.
- 5) The presence and severity of chronic respiratory disease and infection.
- 6) The size and appetite of the patient.
- 8) The quantity and quality of food consumed, hence specific dietary factors.

At the mild end of the nutrient deficiency spectrum, CF patients may have depleted stores or low circulating concentrations of a given nutrient, but with no associated signs or symptoms. More pronounced deficiencies lead to metabolic abnormalities, structural changes, functional disturbances and frank clinical malnutrition.

Nutritional Concerns in Cystic Fibrosis

Because CF affects the nutritional status of the patient so broadly, many components of the diet are of concern, including calories, protein, fat, fat-soluble vitamins and several minerals. The usual CF patient with malabsorp-

tion must take pancreatic enzyme supplements with each meal in order to enhance (but, unfortunately, not normalize) the intestinal uptake of fat and protein. Because stomach acid inactivates pancreatic enzymes, a major advance in the past decade has been the development of coated, pH-sensitive enzyme microspheres available in capsule form which are much more effective than previous products.³

Macronutrients

• **Calories.** Malabsorption, chronic infections and other complications generally increase the total energy requirements in the CF patient. In contrast to the usual textbook description of the voracious appetite of the child with CF, a number of dietary surveys indicate that CF patients actually eat less than normal. Researchers found that on the average CF patients consume only about 80% of the recommended daily amount of calories in spite of increased caloric requirements created by CF and its complications.⁴ An increase of 50%-100% in caloric intake is recommended for the CF child, although occasionally, a child with CF can grow and develop normally on no more calories than the Recommended Dietary Allowances (RDA).

• **Protein.** The major risk of protein deficiency in CF patients occurs during the first year of life when the average requirement is three times as great as in adulthood—1.5 g/kg body weight per day in contrast to the adult minimum requirement of about 0.5 g/kg body weight per day. Human breast milk, which is relatively low in protein (7% of calories), and soy-based formula have been particularly associated with hypoproteinemic edema and growth retardation.⁵ It is recommended that protein should provide about 15%-20% of total daily caloric intake for CF patients with pancreatic insufficiency.

• **Fat.** Some restriction of lipid intake has often been recommended for CF patients in an attempt to reduce the abdominal symptoms of malabsorption. However, dietary fat is recognized as an important high-density source of calories, as improving the palatability of food, and for providing essential fatty acids (EFA) particularly linoleate. Therefore, the traditional tendency to restrict fat consumption of CF patients might cause adverse nutritional consequences, including a deficiency of fatty acids. Because EFA cannot be adequately synthesized by the body if they are not supplied in the diet, certain processes may be impaired, including growth, the production of biological membranes and the functioning of essential metabolic pathways, such as those involved in prostaglandin synthesis.

A number of investigators have demonstrated an altered fatty acid composition in CF patients.^{6, 7, 8} Some

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have postulated that the different fatty acid composition is related to the basic metabolic defect in cystic fibrosis. Yet others have reported that fatty acid composition in CF patients is similar to changes noted in other patients as a consequence of malabsorption of dietary deficiencies. Most of the recent observations indicate that the alterations of fatty acid composition in CF patients are secondary to inadequate linoleate absorption due to maldigestion and/or inadequate dietary fat.⁸ Thus, CF patients without malabsorption have a normal fatty acid status.

Attempts to provide fatty acid supplementation to CF patients have yielded variable results. Intravenous administration of linoleate-enriched lipid solutions results in only a temporary improvement in EFA profile and would have to be administered two to three times per week to maintain improvement. Attempts at oral supplementation of linoleate to correct deficiencies have also led to variable results. Corn oil (1 g/kg/day) given with meals resulted in improved blood fatty acid profiles, but the supplemented patients did not appear to improve clinically as a result.⁹ Safflower oil, another good source of linoleate, given in a similar dose to children on a daily basis for one year also had disappointing results.¹⁰ In a more recent study by investigators using a triglyceride emulsion containing 54% linoleate and given daily in a volume that supplied 7% of calories as EFA, plasma levels were normalized in compliant patients.¹¹

It is recommended that fat supply 40%-50% of total daily caloric requirements, as long as the patient can tolerate this amount without unbearable gastrointestinal symptoms, such as crampy abdominal pain.

Fat-Soluble Vitamins

- **Vitamin A.** A number of investigators have reported vitamin A deficiencies in CF patients that have been variously associated with clinical abnormalities, including keratinizing metaplasia of the bronchial epithelium, xerophthalmia, and night blindness.^{2, 12}

Several mechanisms for vitamin A deficiency have been suggested that range from a defect in the mobilization/transport system associated with liver disease in CF to decreased levels of retinol-binding protein. However, no clear explanation has yet been presented. Because more work needs to be done to elucidate vitamin A metabolism in CF, it is difficult to recommend a specific supplementary dosage that will provide sufficient nutrient value without reaching toxic levels. It seems reasonable that CF patients with malabsorption problems take 5,000 to 10,000 IU per day of vitamin A to supplement their diets. The water-soluble emulsified form of vitamin A appear to be more effectively absorbed by CF patients than the natural, fat-soluble form.¹³ Often, adequate levels of circulating retinol may be maintained by a daily multivitamin preparation, thereby eliminating the need for a separate supplement.

- **Vitamin D.** Bone demineralization is not uncommon in adolescents and young adults with CF.¹⁴ Although a number of studies have suggested that vitamin D may not be normally absorbed in CF patients, none have shown clinical evidence that rickets results, and none of the

studies have been adequately controlled for subject exposure to sunlight.² Based on the currently limited knowledge of vitamin D absorption and utilization in CF, no additional supplementation is recommended for CF patients beyond the 400 IU of vitamin D contained in a daily multivitamin supplement. It is extremely important, however, that these patients consume a diet providing abundant calcium, which means that milk is mandatory for most patients.

- **Vitamin E.** Although erythrocyte instability, neurological lesions and myopathies are potential consequences of vitamin E deficiency in cystic fibrosis, most studies have dealt with hematologic status.¹⁵ One researcher reported five infants with CF who developed hemolytic anemia associated with low vitamin E levels.¹⁶ The effects of vitamin E deficiency and repletion on various hematological indices have been studied in older CF patients.¹⁷

Unsupplemented CF patients with pancreatic insufficiency invariably had significant reduction in their plasma levels of alpha-tocopherol and alpha-tocopherol/triglyceride and alpha-tocopherol/total lipid ratios. Also, erythrocytes from these vitamin E-deficient patients demonstrated increased susceptibility to oxidation as assessed by the *in vitro* peroxide hemolysis test. Despite the observation of normal hemoglobin and hematocrit values, RBC counts and reticulocyte counts, determination of [⁵¹Cr]RBC survival indicated a decreased mean half-life of 22 days compared to 28 days in control subjects. Supplementation with 200 IU/day alpha-tocopheryl acetate resulted in normalization of plasma alpha-tocopherol levels, improvement in values for peroxide-induced hemolysis and correction of [⁵¹Cr]RBC survival times.

Vitamin E supplementation as a watermiscible preparation can prevent tocopherol deficiency in dosages ranging from 50 IU/day for infants to 200 IU/day for adults.

- **Vitamin K.** Vitamin K deficiency has not been routinely demonstrated in patients with CF. Thus far, only infants with CF and those patients with extensive biliary cirrhosis are expected to have prolonged prothrombin times.¹⁸ These children should be treated with vitamin K supplements to improve blood coagulation. A daily dose of 50-100 ug daily or 2.5-5 mg weekly has been recommended.

Minerals

Macrominerals of concern in cystic fibrosis include calcium, phosphorus and especially sodium. Sodium is of concern in CF patients because of its abnormally high content in their sweat. In hot climates, salt depletion can be catastrophic, leading to severe hyponatremic dehydration and shock. However, moderate ambient temperature results in a relatively small sodium loss through sweat.

Adolescents and adults with CF may require two to four times the sodium required by their healthy counterparts. Although it might be assumed that CF patients require daily sodium supplements to compensate for excessive loss through sweat, the average American diet

contains as much as 10 times the amount of sodium needed, even for growing children. Because the American diet contains an excess of sodium, CF patients generally do not need a dietary supplement unless they are exposed to environmental conditions that produce profuse sweating over a long period of time. In these instances, it is preferable to take salt tablets rather than develop the habit of using the salt shaker aggressively.²

Calcium needs can be met by adequate consumption of dairy products. Milk is particularly important and whole milk should be routinely recommended; if pH-protected pancreatic enzyme microspheres are taken, many CF patients tolerate whole milk and other fatty foods.

Nutrition Guidelines in Cystic Fibrosis

Although nutritional status is a major consideration in the treatment of the patient with cystic fibrosis, it has not been proven that nutritional status can significantly influence the overall course of the disease. Nevertheless, there is sufficient information to indicate that deficiencies can occur in caloric intake, fat-soluble vitamins, essential fatty acids and possibly protein and some minerals. As such, general guidelines include variety in daily food selection with a balance between the four major food groups, avoiding an excess of any one food or nutrient. Fiber may be included in moderate amounts. A regular program of physical activity should be incorporated into dietary planning. Most CF patients should also take a daily multivitamin supplement.

Summary: The goal of nutritional care for the CF patient should be to support normal growth and development, even if the patient has pancreatic insufficiency. By optimizing nutritional habits, using potent pancreatic enzyme supplements effectively and treating patients with appropriate micronutrient supplements, physicians should be able to prevent malnutrition and enhance the general health of cystic fibrosis patients.

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Read this like your life depends on it.

Breast cancer found early and treated promptly has an excellent chance for cure. About a week after your period, practice this self-examination.



1. In bath or shower.

Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

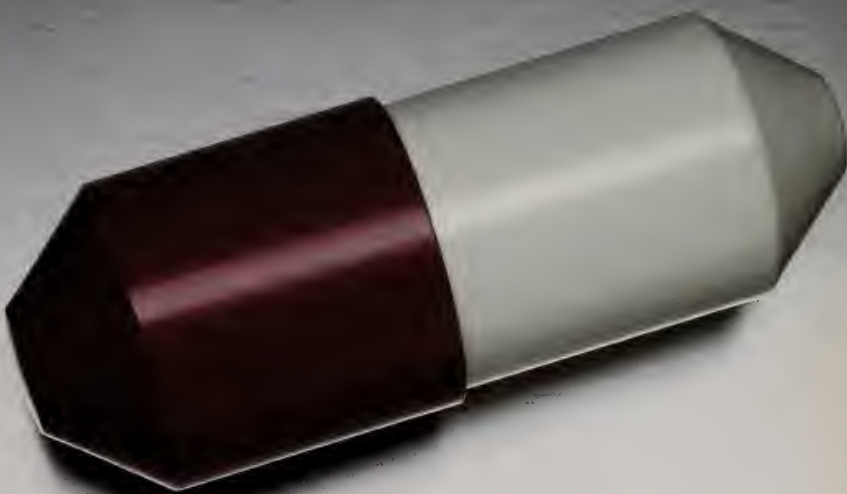
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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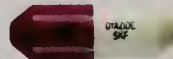
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ARTICULOS ESPECIALES

Mozart's Illness & Death

Peter J Davies, FRACP MRCP (UK)*

Nota Editorial: Esta es la primera vez que el Boletín publica un artículo cuyo asunto "is soon to be a major motion picture." Las conjeturas sobre las causas de la muerte de Mozart son centenarias, pero han vuelto a recibir la atención de miles de personas desde 1979. En ese año se estrenó *Amadeus*, drama del inglés Peter Shaffer, basado en la infundada hipótesis de que el compositor Antonio Salieri provocó la muerte de Mozart. La obra ganó el "Tony Award" como mejor drama de la temporada de 1981 en Broadway, y su transformación al cine está a cargo del director Milos Forman. El artículo que a continuación publicamos estudia sobriamente el historial médico de Mozart y concluye que éste murió de causas naturales. Sin embargo, Francis Carr, en su recién publicado libro, *Mozart and Constanze*, postula que Mozart murió envenenado por un compañero masón, cuya esposa era discípula y, según Carr, amante del músico. Esta hipótesis es aún más indocumentada y fantástica que la de *Amadeus*. La muerte del genio de Salzburgo, como sus obras, parece ofrecer una infinidad de posibilidades de interpretación.—JGRP

The composer Wolfgang Amadeus Mozart died towards the end of his thirty-fifth year, at his rented apartment in Vienna, in 1791. There has been no agreement as to the cause of his death, and it is inevitable that doubts will persist. That is not to say that a study of his illnesses and death would be futile, since it of interest not only to the many music lovers amongst the medical profession, but also to any doctor who is prepared to accept the challenge, in the light of the shortcomings of clinical diagnosis towards the end of the eighteenth century.

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Mozart was born in Salzburg, Austria, on 27 January 1756, and was the second survivor of seven children. The labour was difficult and there was fear for the survival of his 35-year-old mother. Breastfeeding was not popular, and the infant was fed honey and water, and broth with some patent powder.

Wolfgang became the most famous child prodigy in history. He spent his first five years in a comfortable, happy home, much loved by his parents and sister. His father, Leopold (1719-1787), the son of a bookbinder, was an able violin teacher and composer, and later devoted himself almost entirely to the musical and general education of his son. Wolfgang was to be paraded and exhibited around the Courts of Austria and Europe, and the four tours between 1762 and 1771 occupied seven years of his life. During these travels he was exposed to the many endemic and epidemic diseases of those times. The journeys were usually undertaken in uncomfortable carriages, amidst all extremes of weather and often in unsatisfactory accommodation.

Records and documents

None of Mozart's medical records has survived to the present day and an autopsy was not performed when he died. All the symptoms of Mozart's illnesses were recounted by laymen. Leopold had intended to write a biography of his son, and fortunately much of their correspondence has been preserved. The main sources of the illnesses are from the books of Emily Anderson (1966) and Otto Deutsch (1965). The details of the fatal illness are taken from the early biographies of Niemetschek (1798), Nissen (1828), Holmes (1845) and Jahn (1891). It should be noted that the accounts of the key witnesses of Mozart's death, Constanze Mozart and Sophie Haibel, were penned more than thirty years later for the Nissen biography. An expert opinion was voiced in a more extensive document by the physician, Dr Guldener Von Lobes (1824), who defended Salieri.

Mozart's illnesses

These are summarized in Table 1.

Towards the end of his sixth year Mozart suffered four illnesses, which appear to be related. Thus, on 4 October

TABLE I

Illnesses of Wolfgang Amadeus Mozart			
Date	Place	Symptoms	Diagnosis
14 October 1762	Linz	Catarrh	Streptococcal upper respiratory tract infection
21 October 1762	Vienna	Fever and nodules	Erythema nodosum
19 November 1762	Vienna	"Ailing"	Upper respiratory tract infection
31 December 1762	Salzburg	Fever and polyarthritis	? Rheumatic fever
Mid-February 1764	Paris	Fever, sore throat and 'choking'	Quinsy
20 May 1764	London	Ill for 10 days	Tonsillitis
August 1765	Lille	Very bad cold	? Quinsy
15 November 1765	The Hague	Serious febrile illness	Typhoid fever
12 November 1766	Munich	Fever and polyarthritis	? Rheumatic fever
26 October 1767	Olmütz	Epidemic	Smallpox
30 March 1770	Florence	Cold	Upper respiratory tract infection
January 1772	Salzburg	Jaundice	? Viral hepatitis or yellow fever
20 February 1778	Mannheim	Temporary indisposition	Upper respiratory tract infection
10 May 1781	Vienna	Fever and malaise	Upper respiratory tract infection
May-June 1783	Vienna	Bad cold	? Tonsillitis
August 1784	Vienna	Fever, joint pains, abdominal colic and vomiting	Schonlein-Henoch syndrome
April 1787	Vienna	Unknown: ? recurrence of 1784 illness	? Schonlein-Henoch syndrome
April-August 1790	Vienna	Headache, joint pains and malaise	? Schonlein-Henoch syndrome

1762, Leopold wrote that Wolfgang suffered catarrh during the journey on the Danube from Linz. Seventeen days later, in Vienna, Mozart became ill with fever and a few painful, tender, very red and slightly raised spots, the size of a Kreutzer (a coin the size of an old English penny). These lesions were distributed over his shins, elbows and buttocks. Over a period of a week they increased in size but not in number. Wolfgang was kept in bed for eleven days and treated with Pulvis Epilepticus Niger, and Margrave Powders. Leopold had written an excellent description of erythema nodosum, and the attending physician is to be forgiven for his mistaken diagnosis of "a kind of Scarlet Fever", since it was not until forty-six years later that Robert Willan (1808) first described erythema nodosum. On 19 November Mozart was ailing again. Soon after his return to Salzburg, on 31 December 1762, he was put to bed with fever and had rheumatism in his feet, so that he was unable to stand. The above sequence is suggestive of streptococcal infection complicated by erythema nodosum and rheumatic fever. A diagnosis of primary tuberculosis was suggested by Rothman (1945), but this seems less likely in view of subsequent events.

Mozart suffered recurrent upper respiratory tract infections throughout his life, and the more severe of these were probably due to tonsillitis. It sounds as though he developed quinsy in Paris, in February 1764, when Leopold wrote that Wolfgang "was ill in bed for four days with sore throat, cold, very high fever, and in danger of choking". Leopold's favourite household remedies for treating fever included Black and Margrave Powders, violet juice, and tamarind water.

In the spring of 1765, the two Mozart children were stricken with a serious febrile illness whilst at The Hague, Holland. Maria Anna (Nannerl) had caught "a cold" on 12 September. After a few days she had improved, but on 26 September she developed chills and fever and went to bed. Leopold noted that her throat was inflamed and sent for Dr Haymann, who bled her on 28 September with improvement of her pulse. However, the fever persisted and her condition deteriorated so that she became delirious. She was feared lost and anointed by a priest on 21 October. On the following day Professor Thomas Schwenke was summoned in consultation. Vague descriptions of a skin rash ("boils") and pneumonia ("pocks on the lungs") were given. However, she improved and by mid-November was on the way to recovery. On 15 November Wolfgang was also afflicted. Leopold wrote: "Over the next month it made him so wretched that he was not only unrecognisable, but had nothing left save for his tender skin and his little bones. I had to take much care of his mouth. Most of the time his tongue was like dry wood, and dirty, so that it had constantly to be moistened. Three times his lips lost their skin, and became hard and black. By the middle of January, he was recovering and able to walk unaided". Throughout these illnesses, the Mozart parents remained, in their turn, at the sick child's bedside, in six-hour shifts. I must disagree with the diagnosis of streptococcal infection (Scarlett 1964) and typhus fever (Katner 1969, Fluker 1972). The prolonged fever, severe toxæmia, slow pulse, delirium, skin rash, pneumonitis, haemorrhagic exfoliation of the oral mucous membrane and the prolonged convalescence all compound to make endemic

typhoid fever the likely diagnosis, as supported by Clein (1959) and Shapiro (1968).

During his tenth year, in Munich, Mozart was ill in bed from 12 to 21 November 1766, with fever and rheumatism. He was unable to stand on his feet or to move his toes or knees. Leopold wrote that his illness was similar to the one in Salzburg, in January 1763 (? rheumatic fever).

Mozart contracted smallpox and was laid up in Olmütz from 26 October to 10 November 1767. A serious epidemic of smallpox was raging in Vienna at that time. Nannerl later wrote that her formerly handsome brother became disfigured after the smallpox, and that during his convalescence he was taught card tricks and given fencing lessons, much to his delight.

Wolfgang and Leopold arrived in Salzburg after their second Italian tour on 15 December 1771, and Wolfgang had composed his Symphony in A Major (K114) by 30 December. Nannerl, in 1819, wrote that her brother suffered a serious illness soon after the composition of this Symphony, and that during his recovery he looked sickly and very yellow. She referred to a three-length oil painting in which these latter features were evident. This illness was presumably associated with jaundice, and could have been yellow fever, which was endemic in Italy at that time, or viral hepatitis: the long incubation period favours the latter.

Mozart's mother died in Paris aged 57, on 3 July 1778, after a month's febrile illness with headache, shivers, diarrhoea, deafness, hoarseness and eventual delirium and coma. She had been ailing at Mannheim in mid-December, and troubled with a recurring cough. She was bled a little less than two platefuls, and dosed with powder in wine. Although she craved fresh water this was withheld on medical advice. The attending doctor had diagnosed internal inflammation, and the death certificate stated heart disease. The actual cause of her death is not clear (? typhoid fever or tuberculosis).

Mozart's illness in Vienna in August 1784 provides an important clue to the possible cause of his mysterious death. He was very ill and unable to travel to St Gilgen for his sister's wedding. On 23 August, whilst attending Paisiello's opera ("Il re Teodoro in Venezia") at the Burgtheater, he perspired so profusely that his clothes were drenched, and he left early. He wrote to his father: "Four days running, at the very same hour, I had a fearful attack of Colic, which ended each time in violent vomiting. I have therefore to be extremely careful. My Doctor is Sigmund Barisani, who since his arrival in Vienna, has been almost daily at my Rooms. People praise him very highly". There was no mention of renal tract symptoms or rash, but unfortunately Mozart's letter to his father with the details of this illness has been lost. The above information is given in a letter from Leopold to Nannerl, dated 14 September 1784. In this letter, Leopold also says, "so, not only my Son, but a number of other people caught a rheumatic inflammatory fever, which became septic when not taken in hand at once". Mozart remained ill till the middle of September.

Several authors (Schenk 1955, Clein 1959, Scarlett 1964, Fluker 1972) have diagnosed renal colic due to renal calculus, or acute pyelonephritis or pyonephrosis.

However, it is to be emphasized that such renal disorders would not be contracted during an epidemic. Shapiro (1968) diagnosed a severe attack of rheumatic fever, and such a diagnosis is compatible with the known symptoms, limited though they may be. But what if Mozart subsequently developed chronic renal failure? It is my view that Mozart at this time suffered a streptococcal throat infection and that this was complicated by the development of Schonlein-Henoch syndrome. Furthermore, Mozart at this time developed glomerulonephritis, the disease which eventually caused his death.

During his illness in April 1787, Mozart was again attended by his childhood friend, Dr. Sigmund Barisani, who was by then a senior physician. It has been assumed that this was a recurrence of the 1784 illness, but the details are unknown. On 14 April 1787, Barisani wrote in Mozart's album:

"Do not forget thy friend, whose happiness and pride it is to know he served thee twice to save thee for the world's delight! This boast is yet surpassed by joy and pride to know thou art his friend, as he is ever thine."

This illness probably prevented him from attending his father's funeral. Leopold had died in Salzburg aged 68, on 28 May 1787, possibly after a coronary thrombosis (Juhn 1956). Later that year, on 3 September, Dr. Sigmund Barisani died quite unexpectedly aged 29.

During the spring and summer of 1790 Mozart was chronically depressed and frequently ill. The symptoms were mentioned in his letters to Michael Puchberg. During the last four years of his life, the composer wrote nineteen pitiful begging letters to this wealthy merchant and fellow brother Freemason, asking him for loans of money. On 8 April he wrote, "I would have gone to see you myself, but my head is covered with bandages due to rheumatic pains, which make me feel my situation still more keenly"; and in early May, "I am very sorry that I cannot go out and have a talk with you myself, but my toothache and headache are still too painful, and altogether I still feel very unwell".

On about 6 June he went to Baden for a few weeks to stay with his wife, who was taking the cure there. On 14 August he wrote: "Whereas I felt tolerably well yesterday, I am absolutely wretched today. I could not sleep all night from pain. I must have got overheated yesterday from walking so much, and then, without knowing it, I have caught a chill. Picture to yourself my condition — ill and consumed with worries and anxieties". These symptoms are too vague to permit accurate diagnosis. However they are consistent with low-grade tonsillitis, perhaps associated with cervical adenitis. Recurrent arthralgias of two or three days' duration are common in Schönlein-Henoch syndrome (Bywaters *et al.* 1957).

Melancholia

Mozart had an obsessional, immature personality which had been moulded by his insulated upbringing. As a child he was completely dependent upon his father, but he married Constance Weber on 3 August 1782 in open defiance of Leopold's wishes. There were six children of whom only two sons survived to maturity. Constance

tolerated her later pregnancies poorly and was frequently ill during the period 1789-91. She was sent to Baden for a health cure on four occasions. Mozart borrowed money to pay for these cures, and from 1788 onwards they lived a hand to mouth existence. Mozart remained fond of his wife, but their domestic affairs were hopelessly disorganized and extravagant. During their nine and a half years of married life they occupied eleven different apartments. Mozart was appointed Chamber Musician to the Emperor on 6 December 1787, but the salary of 800 florins a year was inadequate. After his production of "Figaro" and "Don Giovanni" he was snubbed by the fickle Viennese aristocracy. He suffered a great deal from his unattractive appearance — he was about five feet tall, with an over-sized nose that was frequently caricatured, and his face was disfigured as a result of smallpox. His external ears were deformed (Berstrom 1979), but is hearing is said to have been remarkably acute. Mozart was fond of punch, and drank beer or wine, usually in moderation.

His mother's death in Paris was the first that he had witnessed and he suffered transient fits of melancholia after it. It is interesting that he became preoccupied with death in his last year. During the summer of 1788 Mozart was troubled by recurrent "black thoughts which I banish by a tremendous effort". However, with an astonishing burst of creative activity he composed the three last great symphonies on 26 June, 25 July and 10 August. The following year, in July 1789, at the time of his wife's illness (probably a varicose ulcer), he appeared to be profoundly depressed. During 1790 his depression became more persistent so that it interfered with his output of music. During his last eleven years Mozart completed 295 compositions at an average of 27 per year (Kochel 1979). It has been estimated that these works correspond in writing time alone to an eight-hour day for the same span of time (Franken 1980). It is interesting that the two "lean" years were 1784 (18 compositions) and 1790 (10 compositions). On the other hand, his best years in terms of output were 1788, 1782 and 1791 during which he completed 43, 35 and 34 compositions respectively. It is little wonder that he rose at 6 am and often worked through till 2 am.

Mozart's depression is discussed by Franz Reichsman (1981), who points out that Mozart's immature personality was particularly vulnerable to object loss. Although these initial episodes of melancholia may have been reactive to stress in a vulnerable personality, more definite evidence of organic disease made its appearance in his last year.

Cerebral vascular disease and chronic renal failure

Mozart suffered chronic ill health during the last six months of his life, and the details are summarized in Table 2. His depression worsened and he became preoccupied with thoughts of death. In conjunction with this there was a change towards a paranoid personality, and his emotional responses were labile. Early in August 1791, Anton Leitgeb visited Mozart to commission a requiem mass, and he insisted that the identity of the anonymous patron (Count Walsegg-Stuppach) was to remain secret. The composer saw him "as a gaunt all

stranger in a grey cloak". Mozart subsequently became tormented with delusions that he had been poisoned and also that he had been commissioned to write his own requiem.

TABLE II

Mozart's Chronic Ill Health and Fatal Illness in 1791, and Hypotheses as to Cause of Death

Chronic ill health (latter half 1791)

Depression, personality change, paranoid delusions, headache, blackouts, anaemia, weight loss

Fatal illness (20 November-5 December 1791)

Epidemic, duration of 15 days, fever, painful swelling of hands and feet, vomiting, diarrhoea, partial paralysis, exanthem, venesection(s), terminal coma with paralysis of conjugate gaze

Diagnoses: "Un deposito alla testa" (Closset); "Hitziges Frieselfieber" (Sallaba); "Rheumatic inflammatory fever" (Guldener Von Lobes)

Hypotheses as to cause of death

Tuberculosis; typhus fever; septicaemia; poisoning-(a) by Salieri, (b) iatrogenic from treatment of syphilis, (c) by the Freemasons; uraemic coma; acute rheumatic fever; venesection(s); bacterial endocarditis

The history of recurrent violent headache and blackouts is of much more discriminatory value. James Collier included Mozart among the famous men who were proven or reputed epileptics (Bett 1956), however there is no record of convulsions. Holmes (1845) wrote: "He sunk over his Composition into frequent swoons, in which he remained for several minutes, before consciousness returned". Jahn (1891) wrote: "These fainting fits exhausted his strength and increased his depression".

Mozart conducted the premiere of his opera "La Clemenza Di Tito" (K621) before the Emperor and Empress on 6 September 1791. Niemetschek (1798), who was an eye witness, wrote: "Mozart was ill in Prague, and dosed himself ceaselessly. His colour was pale, and his countenance sad, although his merry sense of humour often bubbled into jesting, in the company of his friends".

Constance Mozart, upon her return from Baden in mid-October, was shocked to see the deterioration in his health, and noted his worsening pallor, enervation and weight loss. She took away the score of the requiem, with which he was preoccupied, and called in Dr. Franz Closset. Mozart recovered sufficiently to be able to compose his "Little Masonic Cantata" (K623), which he conducted at the inauguration of the "New Crowned Hope" Lodge, on 18 November.

All of the above symptoms in a 35-year-old man are nicely explained by a diagnosis of hypertensive cerebral vascular disease on the basis of chronic renal failure (Hughes *et al.* 1954). Alas, Mozart's blood pressure was never recorded, since a noninvasive method of measurement was not invented until 1876 by Ritter Von Basch (Lyons 1979). Nor is there any record of urinalysis, since Richard Bright had not yet written his classic account of the significance of albuminuria in the diagnosis of renal disease (Bright 1836). However, it is to be noted that Bright included depression amongst the clinical features of Bright's disease. Other authors (Greither 1956, Clein 1959, Scarlett 1964, Fluker 1972) have also diagnosed chronic renal failure as the cause of Mozart's ill health during 1791, but have been less expansive over the mental symptoms.

Mozart's fatal illness

Mozart took to his bed for the last time on 20 November 1791. His final illness had been contracted during an epidemic, probably at the Lodge, on 18 November, and lasted 15 days. The details are listed in Table 2. It was associated with a high fever and much sweating. During the night he complained of pain on moving in bed, and his wife noted that his feet and hands were quite swollen. The swellings were therefore due to polyarthritis. There were recurrent attacks of violent vomiting, especially at night, and later diarrhoea. After a week in bed he was helpless: "Partially paralysed". According to Schack, a family friend, Mozart's weakness was such that he was obliged to be drawn forward whenever he required to sit up in bed. Sophie Haibel and her mother made him night shirts which could be put on him from the front, for he could not turn over in bed because of the swelling. He became hypersensitive to the song of his beloved pet canary, which had to be removed from the next room because it overtaxed his emotions. On 28 November, Closset requested a consultation with Dr. Mathias Von Sallaba (1754-1797), a senior physician at the General Hospital. Sallaba noted an exanthem, for he diagnosed "a heated Miliary Fever". The exanthem was not noted by Constance or Sophie Haibel, so that presumably it caused no itch or sting, and was not present on the exposed parts of Mozart's body. It is likely that Mozart had bed socks on, since the weather was cold. Constance said that a venesection was performed, but did not give any further details.

Mozart remained conscious until two hours before his death, and said that there was a taste of death on his tongue. During the final evening the fever persisted and the composer was anointed. Dr. Closset was summoned, and came from the theatre at about 11 pm. Constance was distraught and hysterical, so that a sedative was administered. Closset ordered Sophie Haibel to apply a towel, moistened with vinegar and cold water, to Mozart's forehead. There followed a violent shuddering (a convulsion) followed by loss of consciousness. Towards midnight, he raised himself, opened his eyes wide, and then lay down with his face to the wall. Sophie Hibel noted that he puffed out his cheeks, and presumed that he was imitating the trumpets and drums in a passage from the requiem. Mozart remained unconscious and died at about 1 o'clock on 5 December. Van Swieten undertook the funeral arrangements, and on 6 December Mozart's body was consigned to a common grave containing 15-20 corpses: no stone marked his resting place in the churchyard of St Mark's.

Testament of Dr. Guldener Von Lobes (1763-1827)

The composer Antonio Salieri (1750-1825) had become senile in the autumn of 1823, and in his madness is said to have accused himself of poisoning Mozart. The poisoning rumour was rife in Vienna at that time. Guiseppe Carpani, a friend of Salieri, exhorted Dr. Guldener to write him a letter which would dismiss the evidence of poisoning and so exonerate Salieri. Dr. Guldener was Chief Physician at the General Hospital,

and he wrote the testament on 10 June 1824. He wrote that Mozart had fallen ill in the late autumn of 1791 "with a rheumatic and inflammatory Fever, which had also attacked a great many of the inhabitants of Vienna at that time", and that several patients had died with similar symptoms to Mozart. Guldener had not personally attended Mozart but he had recalled discussing the case with Closset and Sallaba, with whom he was in daily contact. He said that Closset had diagnosed "*Un deposito alla testa*". He said that a few days before Mozart's death he had met Sallaba, who said positively, "Mozart is lost, it is no longer possible to restrain the deposit". He said that "Mozart died with the usual symptoms of a deposit on the brain, and that there was not the slightest suspicion of poisoning". He said that "the Statutory examination of the corpse, did not reveal anything at all unusual" (Guldener Von Lobes 1824).

"*Un deposito alla testa*"

This translates literally as a deposit in the head. It has been interpreted to mean inflammation of the brain, meningitis, or even encephalitis. Some writers have even read meningovascular syphilis into it. Carl Bär (1966) argued that it referred to rheumatic nodules in the scalp, in support of his diagnosis of rheumatic fever. Thomas Franz Closset (1754-1813) had been physician to the Mozart family since attending Constance in July 1789. He knew Mozart well and had seen the evolution of neuropsychiatric symptoms. It is my view that Closset suspected Mozart to have a space-occupying lesion of the brain, but that he was puzzled by the polyarthritis and exanthem of his fatal illness and therefore sought help from Sallaba.

"*Hitziges Frieselfieber*"

This is the diagnosis in the Register of Deaths and it translates simply as a heated miliary fever. This is entirely nonspecific and simply refers to an illness associated with fever and exanthem (Katner 1969, Franken 1980).

Review of the literature

The hypotheses as to the cause of Mozart's death are listed in Table 2

Tuberculosis

George Nikolaus Nissen (1761-1826) married Constance Mozart in 1809, and with her help wrote a biography of Mozart. This work was completed by the Dresden physician, Johannn Feuerstein, who diagnosed consumption as the cause of Mozart's death. A remote case can be made for a diagnosis of tuberculosis, according to the following sequence: Mozart developed cervical tuberculosis in October 1762 and this was responsible for his erythema nodosum; in August 1784, he developed renal tuberculosis which presented with renal colic, and which recurred in 1787; his chronic illness was due to a cerebral tuberculoma and he died of miliary tuberculosis. Although it is well documented that several years may elapse between the onset of renal colic and the subsequent diagnosis of advanced renal tuberculosis (Wechsler *et al.*

1960), the above sequence of events seems far too remote for further consideration. Nor does it take into account the epidemic nature of the illness in 1784 and the fatal illness.

Typhus fever

Early biographers such as Dr. F Gehring (1883) interpreted "*Hitziges Frieselfieber*" as indicating malignant typhus fever. However such a diagnosis does not take into account the chronic nature of the composer's illness.

Septicaemia

Shapiro (1968) diagnosed death from streptococcal septicemia complicated by acute renal failure, but once again the same objection is lodged. Professor F Franken (1980) diagnosed an acute infectious disease with death from a toxic carditis, and argued that there was no convincing evidence of chronic ill health. He denied Mozart's depression and said that he was really cheerful up until shortly before the time of his death. He argued that Mozart's incredible productivity of composition denied the existence of chronic illness. I must disagree strongly, and have already presented convincing evidence in support of cerebral vascular disease and chronic renal failure.

Poisoning

On 17 July 1829, Mary Novello wrote in her travel diary that, six months before his death, Mozart had told his wife that he was convinced that he had been poisoned with Acqua Toffana (which contains arsenic and lead oxide). The rumours that Salieri had poisoned Mozart have already been mentioned. In 1953 the Russian, Igor Belza, wrote a book expanding this theory. However, the German physician, Dr. Dieter Kerner, is the most enthusiastic advocate of the poisoning theory. He has written over 30 papers in which he presents medical and historical arguments. Kerner explains Mozart's chronic ill health in the latter half of 1791 as being due to chronic mercury poisoning. The final lethal dose was administered at the end of November, and this resulted in a nephrotic syndrome and death from renal failure. First, it was supposed to have been Salieri, then Mozart was supposed to have treated himself with quicksilver against an alleged attack of syphilis, and thus poisoned himself (Kerner 1969, Katner 1969). A venereologist, Dr. J L Fluker (1972), concluded that there was no evidence that Mozart suffered from syphilis. In 1966, Belza *et al.* proposed that Mozart was poisoned by his fellow Masons by sublimate, because he had betrayed Lodge secrets in his opera "*The Magic Flute*". The poisoning theory was well refuted by the Swiss authorities, Ackerknecht & Isler (1968). They argued that Mozart's swellings were due to polyarthritis and not a nephrotic syndrome. Nor was there any evidence of the tremor which is such a feature of chronic mercury poisoning. It is to be remembered that emetics and purgatives were commonly prescribed at that time.

Uraemic coma

The pioneer of the uraemic theory was Dr. J Barraud (1905), who diagnosed post-scarlet fever nephritis aggravated by years of overwork. The diagnosis of uraemia was further developed by others (Greither 1956, Clein 1959, Scarlett 1964, Carp 1970, Fluker 1972). The underlying cause of the uraemia was either post-streptococcal nephritis or chronic pyelonephritis. All these authors have attributed Mozart's swollen hands and feet to nephrotic oedema. There is good evidence that this is not so, and that Mozart suffered with polyarthritis. Nor do the above authors explain the epidemic nature of Mozart's fatal illness. Charles Roe (1971) concluded that Mozart died of congestive cardiac failure, complicating renal disease, and that in addition he probably had rheumatic heart disease.

Acute rheumatic fever

In 1906 Bókay diagnosed rheumatic heart disease, and subsequently a diagnosis of death from acute rheumatic fever was developed by Bär (1966) and Katner (1969). This diagnosis accommodates the epidemic nature of the final illness and accounts for the acute polyarthritis. However, an exanthem is rare in rheumatic fever, and such a diagnosis does not account for the chronic ill health of 1791. Nor does it explain the neurological symptoms of the fatal illness. Mozart showed no evidence of chorea. It is to be remembered that it was not until 1819 that Laennec wrote his classic paper on auscultation (Osler 1907).

Venesection

Carl Bär has studied the practice of venesection, which in the late eighteenth century tended to be performed in all cases of inflammation and fever. On the basis of calculations made by Bär, with regard to Sallaba's patients, he concluded that the small-built Mozart could have been drained of four or more pints, and that this would have caused 'Haemorrhagic Shock' (Bär 1966, Katner 1969). Such estimates to me seem excessive, but I would add that venesections are contraindicated in patients with anaemia due to chronic renal failure.

Bacterial endocarditis

Bacterial endocarditis is worthy of mention and was included in Clein's (1959) differential diagnosis. One could argue that Mozart's illness in 1784 was due to severe rheumatic fever, and that subsequently he developed chronic rheumatic carditis. In May 1790 Mozart complained of toothache, and it is possible, though not recorded, that he subsequently underwent a tooth extraction, which caused bacterial endocarditis. As a result of septic emboli, he then developed a frontal lobe abscess with eventual death from septicemia and renal failure. However, the course seems too prolonged and it does not explain the epidemic nature of the fatal illness.

Schönlein-Henoch purpura

This diagnosis solves the mystery and ties up the loose ends. Mozart contracted a streptococcal infection while attending the Lodge on 18 November 1791, amidst an epidemic. He was stricken with anaphylactoid purpura two or three days later, and this caused the acute polyarthritides and exanthem. The purpura was asymptomatic, and probably confined to his lower limbs, since it was not noted by his wife or Sophie Haibel. Gairdner (1948) reported that the latent interval in recurrent attacks between upper respiratory tract infection and symptoms was shortened to between one and seven days. No doubt Mozart's vomiting and diarrhoea, and possibly the venesection(s), aggravated his renal failure. The chronic renal failure was due to chronic glomerular nephritis, which had been contracted during his first attack of post-streptococcal Schönlein-Henoch purpura in 1784. There were probably further recurrences in 1787 and 1790. Cream *et al.* (1970) documented that some adults with this condition develop recurrent attacks over many years, and that at times the symptoms of such recurrences are vague (e.g. fever, arthralgia, fatigue and headache). Mozart had such symptoms during the spring and summer of 1790.

J L Fluker (1972) noted that Mozart's tendency frequently to dose himself with proprietary medications may have further damaged his kidneys. It should be noted that 29 of 77 adults cases of Schönlein-Henoch purpura had taken proprietary medications within three weeks of onset of symptoms in the series of Cream *et al.* (1970), although there was insufficient evidence to prove a causal relationship.

Cerebral haemorrhage

After a week in bed Mozart was helpless and partially paralysed, and unable to sit up unaided. It is my view that the Schönlein-Henoch purpura had caused an exacerbation of hypertension, which contributed to his nocturnal vomiting, and caused a hemiparesis. About two hours before his death he convulsed and became comatose. Then, an hour later, he attempted to sit up, opened his eyes wide and then fell back with his head turned to the wall. His cheeks were puffed out. These symptoms suggest paralysis of conjugate gaze, and facial nerve palsy. They are consistent with a massive haemorrhage in either one of the frontal lobes or brain stem. It is interesting that the second case of Gairdner (1948), a 4 1/2-year-old child with Schönlein-Henoch purpura, died in coma. Autopsy showed evidence of subacute glomerular nephritis and scattered haemorrhages throughout the left occipital lobe. Histology of the arterioles, meninges and superficial grey matter showed evidence of necrotizing arteritis.

Streptococcal bronchopneumonia

On the evening before his death, Mozart was suffering with high fever and drenching sweats. Bronchopneumonia is frequently the immediate cause of death in patients with uraemia, and it usually develops when the patients are already moribund (De Wardener 1963).

Summary

Throughout his life Mozart suffered frequent attacks of tonsillitis. In 1784 he developed post-streptococcal Schönlein-Henoch syndrome which caused chronic glomerular nephritis and chronic renal failure. His fatal illness was due to Schönlein-Henoch purpura, with death from cerebral haemorrhage and bronchopneumonia. Venesection(s) may have contributed to his death.

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Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g., driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive.

Drug Dependence: Use caution in addiction-prone patients.

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of carisoprodol.

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances.

Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock.

DOSAGE AND ADMINISTRATION: *Adults* — One 350 mg tablet 3 times daily and at bedtime.

OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used successfully with related drug, meprobamate.

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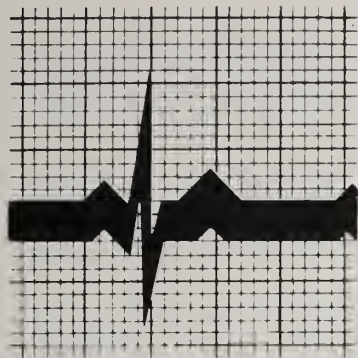


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ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, MD, FACC

This 58-year-old female complained of dyspnea, palpitations, chest discomfort, orthopnea, paroxysmal nocturnal dyspnea and leg edema. There were marked cardiomegaly, biventricular enlargement and pulmonary vascular engorgement. Digoxin, nitrates and a diuretic were prescribed. A dilated cardiomyopathy was diagnosed. Serum potassium was 3.1 - 4.5 meq/L. Digitalis intoxication was considered in October, 1981 (digoxin level was 1.39 ng/ml).

Many electrocardiograms (ECG) were obtained during 1981 (Figures 1A, 1B, 2, 3).

Figures 1A, 1B

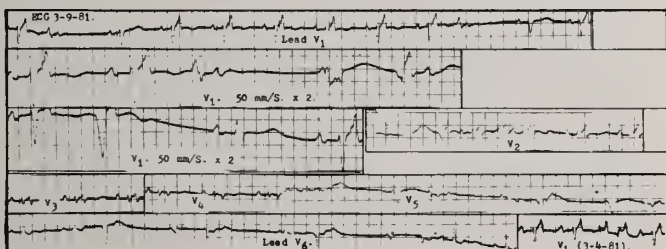
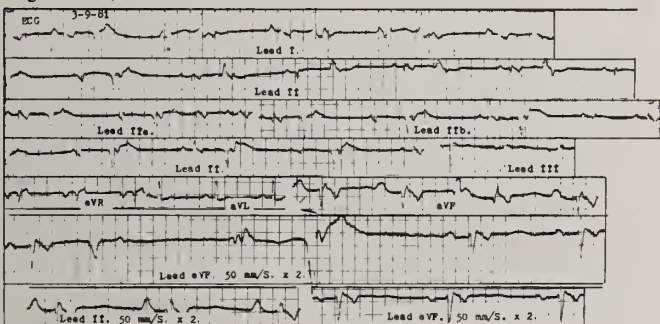


Figure 2

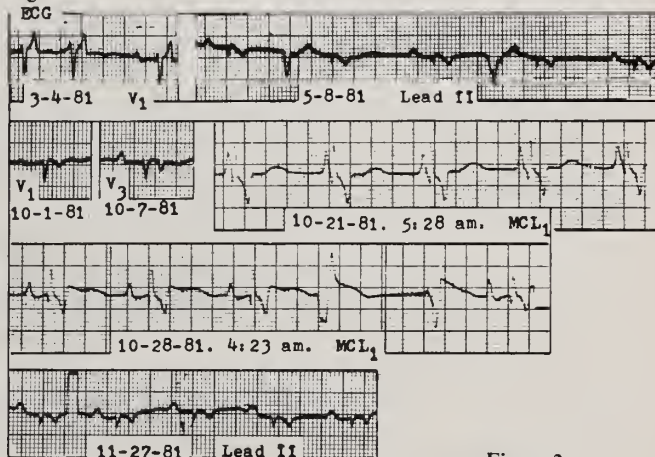
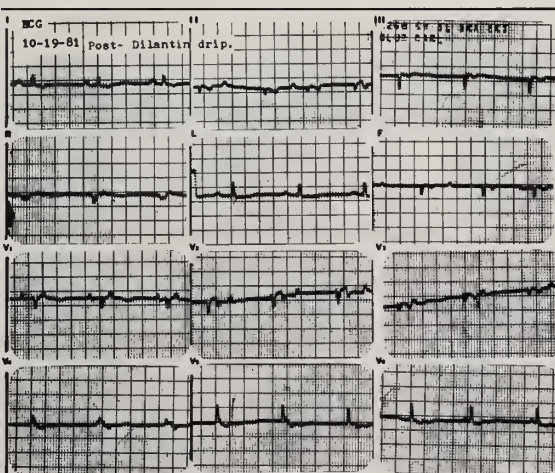


Figure 3



Questions

1. What are the arrhythmic diagnoses?
2. Give a differential diagnosis.

Description of ECGs

Figures 1A, B. Normal sinus rhythm (NSR). Atrial rate approximately 70 per minute. PR interval 0.17-0.20 S, QRS 0.06-0.08 S, QT 0.20 S. Small QS/tiny r wave in leads II, III, aVF. T waves peaked in aVR, V₁, diphasic in leads I, V₂₋₃, V₅₋₆ and inverted in II, aVF, V₄. Atrial enlargement. Atrioventricular dissociation (AVD).

Multiform ventricular premature beats (VPB) in leads I, II, aVF, V₁, V₅₋₆; bigeminy; nonfixed coupling at times. QR in aVF, V₂; QRs in V₁ (second row). (JPBs may be more likely on the basis of the complexes. Ventricular escape beats (VEB) - third and seventh beats in lead I, third beat in aVF (sixth row), fourth in V₁ (second row), V₅ (third, seventh). Ventricular capture beat (VCB) - lead IIa (fifth).

Interpolated VPB with retrograde concealed conduction in aVF (subsequent longer PR interval).

Junctional premature beats (JPB) - exemplified in lead IIa (fourth), interpolated in V₂ (fourth); paired aberrant in V₁ of 3-4-81; V₆ (fifth and ninth). Their distinction from VPBs is difficult.

Junctional escape beats (JEB) - lead IIa (third), V₅ (fifth), V₆ (fourth), sixth and eighth). Ventricular fusion beats seem less likely. Many of the the VPBs have an inverted wave immediately afterwards suggesting a retrograde P. However, this wave is too close to the sinus P for such-atrial refractory period (ARP). In lead V₁ (top row), the third (1160 ms afterwards) and penultimate (1140ms) beats, and the third beat in the third row (1100 ms) appear as more normal beats with a normal Q-T interval and QRS complex. The JEBs have slightly upright T waves in leads II; so do certain apparently conducted beats (last beat, second row). The last cycle in lead II (fourth row) measures 1290 ms, yet without a subsequent QRS-T change. The QRS contours (qR) of the fifth beat in IIb and the fourth beat in lead II (fourth row) are different from the basic morphology, in that they follow the longest R-R cycles of 1320 ms; yet their T waves are diphasic! Their nature is unsure; and could represent Phase 3 normalization of the QRS- the two sole normal QRS complexes in the entire three figures, the others representing aberrant beats? Thus, the T wave morphologies are not consistently cycle-dependent correlated.

Figure 2. 3-4-81. The second beat is a JPB without subsequent T normalization (pause 840 ms).

5-8-81. First degree atrioventricular (AV) block. Interpolated VPBs (second and fifth), with retrograde concealed conduction (AVD is difficult to exclude). The T wave in V₁ is distinctive on 10-1-81. Isorhythmic AVD exists on 10-21-81, as the P-R distance is short and variable. On 10-28-81, the fourth beat is a VPB followed by a VEB. There are NSR and first degree AV block on 11-27-81.

Figure 3. 10-19-81. Post-phenytoin IV. Possible left anterior hemiblock (LAH). NSR. P rate approximately 63 and the idiojunctional rate 65-66; Q-T 0.20-0.22 S; QS/tiny r in leads II, III, aVF, V₁₋₃; U wave; AVD, slightly accelerated junctional rhythm; VCB with first degree AV block (third beats in leads II and aVF). There is a shorter R - R cycle after the VCBs, due to the sinus

impulse of the VCB discharging the AV node prematurely and resetting its cycle begins again from this point. The pre-and post-capture cycles are less than the sum of two consecutive AV nodal intervals. Also, these beats could be accelerated JEBs.

Discussion

This series of ECGs present several diagnostic considerations and problems.

The Q-T interval depends upon a number of factors, namely: sex, age, heart rate, congestive heart failure, myocardial ischemia, drugs, serum potassium, hydrogen and calcium levels. A short Q-T interval, representing accelerated ventricular repolarization, occurs with a rapid rate, fever, acidosis, thyrotoxicosis, stimulation of sympathetic nerve supply to the heart, digitalis (the commonest), phenytoin and hypercalcemia. Hypercalcemia does this by shortening phase 2 of the action potential (AP). The T wave duration remains unaffected. Hypercalcemia was not recognized in this patient.

An important differential diagnosis is that the prominent positive wave immediately following the QRS complexes (basic and VPBs) is not a short ST segment and T wave, but a retrograde P¹ wave, that is, a reciprocal or echo beat. A retrograde P¹ wave manifests in lead V₁ as a dominantly upright P¹ with loss of the terminal negative component. A strong factor against this possibility is that sinus P waves, dissociated, occur too close to this wave (P¹), remembering that the ARP is 150-360 ms. These early waves are neither likely to be part of the QRS complex.

VPB-induced, cycle-dependent postextrasystolic T wave (inversion, flattening, etc) and Q-T interval (lengthening) changes may occur to explain these findings. Occasionally changes in ventricular repolarization, as primary T wave changes manifest after a VPB pause (especially an interpolated VPB) in the first postextrasystolic beat, and more rarely in the second or third successive sinus beats. This was previously believed to mean organic heart disease, particularly coronary artery disease. More recent studies have not found a correlation with cardiac disease nor left ventricular dysfunction, because postextrasystolic changes occur commonly in normal individuals. This transient asynchrony of ventricular repolarization may be due to asynchronous and gradual adjustments of different APs to the abrupt change in cycle length (a lag in AP shortening); to prolonged ventricular diastolic filling and increased diastolic heart size, mechanical impact against the chest wall after a long pause, contractile changes in the postextrasystolic beat, restriction of coronary blood flow or to an increase in ventricular gradient from the longer cycle length. The frequency of these changes depend on the length of the compensatory pause following the extrasystole.

Bundle branch block may disappear (Phase 3 or Tachycardia-dependent block) after a post-VPB pause.

A post-VPB pause might also alter the environment for and manifestation of a reciprocal beat.

First degree AV block, AVD, accelerated JEB and different coupling, suggest digitalis intoxication.

Overall, the tracings suggest digitalis intoxication, atrial enlargement, LAH, short Q-T intervals, pseudo-myocardial infarction patterns, AVD, AV block, multifocal ventricular and junctional ectopy and escapes, and cycle-dependent, QRS and ST-T wave abnormalities. Electrophysiologic studies during the arrhythmia would have contributed as a diagnostic tool. Digitalis-induced arrhythmogenic after-depolarizations may be the mechanism of the ectopy.

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Resúmenes de La Literatura Médica

PERCUTANEOUS BALLOON VALVULOPLASTY FOR TREATMENT OF CONGENITAL PULMONARY VALVULAR STENOSIS IN IN CHILDREN. Rocchini AP, Kveselis DA, Crowley D, et al. J Am Coll Cardiol 1984; 3:1005-1012

Los autores, de la Sección de Cardiología Pediátrica de la Escuela de Medicina de la Universidad de Michigan, en Ann Arbor, informan su experiencia con la valvuloplastia transluminal con balón de la válvula pulmonar en 7 niños con estenosis pulmonar moderada y severa. Las edades fluctúan entre los 1.5 y 9.9 años.

En todos los casos hubo una disminución significativa en la presión ventricular derecha, en el gradiente del ventrículo derecho a la arteria pulmonar y un aumento en el área valvular pulmonar. Dos pacientes sometidos a ejercicio antes y después de la valvuloplastia tuvieron una reducción marcada en la presión sistólica ventricular derecha y en el gradiente a través de la válvula pulmonar luego del procedimiento. Todos los pacientes toleraron el procedimiento bien, no hubo complicaciones, y 6 de ellos regresaron a sus hogares al día siguiente.

Los beneficios de este procedimiento son múltiples, la valvuloplastia con balón promete ser un método seguro y efectivo en el manejo de la estenosis pulmonar valvular. Sin embargo la liberalización en el uso de esta técnica y su uso como procedimiento de elección en el tratamiento de la estenosis valvular pulmonar requiere mayor información, especialmente en establecer que la eliminación de la obstrucción del tracto de salida ventricular derecho es uno de larga duración.

Rafael Villavicencio, MD, FACC

A CONTROLLED PILOT STUDY OF HIGH-DOSE METHOTREXATE AS POSTSURGICAL ADJUVANT TREATMENT FOR PRIMARY OSTEOSARCOMA. Edmonson JH, Green SJ, Ivins JC, et al J Clin Oncol 1984; 2:152-156

This Mayo Clinic group of investigators present the results of a study performed to determine whether adjuvant chemotherapy with high dose methotrexate is of any advantage to patients undergoing radical surgery for

osteosarcoma. Thirty eight patients who underwent surgery with complete excision of the primary tumor were randomized to either no chemotherapy (20 patients) or chemotherapy with vincristine and high dose methotrexate with leukovin rescue (18 patients).

A five year follow-up showed no significant difference in the outcome of both groups of patients; recurrences and survival were basically the same. This data fails to support that of Jaffe and Holland, who described better long term results in osteosarcoma patients receiving adjuvant high dose methotrexate, than in historical controls who received no chemotherapy.

Editorial Comment:

This important article casts light on several important points for oncologists and surgeons:

1. There is no clear evidence to support the use of adjuvant chemotherapy as a routine in osteosarcoma patients. This is still an investigational problem.

2. The use of historical controls to determine value of adjuvant chemotherapy might be misleading. It may ascribe to chemotherapy-improved outcome of patients, which is actually due to better surgical techniques, earlier diagnosis, and better technologies to detect widespread disease prior to surgery.

3. Controlled clinical trials are needed to determine the therapeutic value of adjuvant chemotherapy for patients with resectable osteosarcoma.

José A. Lozada Román, MD, FACP

HEPARIN-ASSOCIATED THROMBOCYTOPENIA King DJ, Kelton JG, Ann Intern Med 1984; 100:535-540

A review of a group of very complete prospective studies on the platelet-lowering effect of heparin is complemented by the authors own experiences. Heparin-associated thrombocytopenia occurs in about 5% of patients who receive this drug. The incidence is higher with heparin derived from beef than pork-derived heparin. The onset of thrombocytopenia occurs mostly six to twelve days after commencement of heparin treatment. The mechanism appears to be one in which heparin acting as a hapten induces an immune response against the heparin-platelet complex.

Heparin, nevertheless causes platelet aggregation. This latter event might be associated to heparin-associated thrombocytopenia plus arterial thrombosis which is a rare but highly fatal complication of heparin therapy.

Prompt switch to coumadin derivates after initiation of heparin treatment is suggested as a means to prevent 90% of cases of heparin associated thrombocytopenia.

José A. Lozada Román, MD, FACP

CROHN'S DISEASE AND PREGNANCY. Khosla, R, CP Willoughby, Jewell, OP. Gut 25: 52-56, 1984.

La enfermedad de Crohn afecta personas jóvenes con frecuencia y puede ser de preocupación a mujeres con la enfermedad que desean tener hijos. Los autores reportan su experiencia de 20 años con mujeres casadas menores de 45 años de edad con enfermedad de Crohn. De su experiencia con 54 pacientes que llenaban los requisitos del estudio ellos presentan evidencia que favorece las siguientes conclusiones:

1. la tasa de infertilidad (12%) es similar a la de la población en general (10% reportado);
2. la enfermedad de Crohn debe permanecer inactiva durante el embarazo si está inactiva al momento de concepción y es probable que continúe activa durante el embarazo si está activa al concebir;
3. si la paciente necesita terapia con sulfasalazina o prednisona durante el embarazo ambas se pueden utilizar y en su experiencia no se asociaron con efectos nocivos al feto o a la madre.

Angel Olazabal, MD

NORMAL SERUM ANGIOTENSIN CONVERTING ENZYME ACTIVITY IN PATIENTS NEWLY DIAGNOSED OF SARCOIDOSIS. De Remee, RA et al. Chest 1984; 85:45-97.

Los autores buscan en este estudio el significado de un nivel normal de "serum angiotensin converting enzyme activity" (SACE) en los pacientes de Sarcoidosis recién diagnosticados. Ellos dividen los pacientes según el estadio de su enfermedad y así reportan:

Estadio I - 16 pacientes
Estadio II - 1 paciente
Estadio III - 7 pacientes

Todos los pacientes eran de raza blanca, sus edades fluctuaban entre 30-64 años, 8 hombres y 16 mujeres.

Los niveles de SACE en estadio I caían entre 36-57 units/ml. y una media de 44. Los niveles de aquellos pacientes en estadio II y III caían entre 43-57 con una media de 53 units/ml.

Los autores sugieren que los pacientes de Sarcoidosis en estadio I con niveles de SACE normales tienden a tener mejor pronóstico y mayores probabilidades de remisión.

Los autores señalan también que el hallazgo de SACE normal no siempre quiere decir que la enfermedad esté inactiva porque según su experiencia algunos pacientes con SACE normal tuvieron mejoría notable en ciertas anomalías luego de tratarse con prednisona. Los niveles de SACE en estos pacientes disminuyeron significativamente aun dentro de límites considerados normales para la población general.

Los autores terminan su artículo haciendo un resumen del origen del SACE en las personas normales y en los pacientes con Sarcoidosis en cuyo caso el SACE es de un origen doble; vascular y granulomatoso. Aquel de origen granulomatoso es el único susceptible a disminución el tratamiento con esteroides.

Ellos son de la idea que el valor absoluto del SACE en los pacientes con Sarcoidosis es menos importante que el cambio en el nivel de SACE debido a los esteroides recibidos por el paciente.

Ramón Figueroa Lebrón, MD, FCCP

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What can you do for hypertensives like Janet M?

"Scared" of doctors

But insurance physical reveals a diastolic of 104 mmHg.

Career woman

At her peak at 50...no room in her busy schedule for a complicated regimen.

Eats out

Will try from now on to select dishes with fewer calories.

Childhood asthmatic

Hasn't wheezed in forty years.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Janet M represents 4,533 women age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol use has been associated with bronchospasm even in patients with no history of wheezing or dyspnea.³ Unlike propranolol, TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors.⁴ Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Janet M...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)



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ONE TABLET A DAY TENORMIN® (atenolol)

For Janet M...
and virtually
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TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nor epinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)		Maximum Dosage
	15-35	16-27	
<15		>27	50 mg daily
			50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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El 7 de agosto de 1984 dará comienzo el Curso de Repaso Intensivo (REFORFLEX), para médicos que se preparan para los exámenes arriba mencionados.

Este curso cubrirá las Ciencias Básicas y Ciencias Clínicas y la matrícula será limitada a las primeras 100 personas registradas.

Urgimos a los interesados a comunicarse a la mayor brevedad posible con:

Dr. Jorge Ortega Gil
Director Educación Médica Continuada
Escuela de Medicina, Universidad de Puerto Rico
Teléfonos: 753-3830 / 753-3829 / 763-7349



SECCION DE CARDIOLOGIA
DEPARTAMENTO DE MEDICINA
ESCUELA DE MEDICINA
UNIVERSIDAD DE PUERTO RICO

PRESENTAN ANGINA PECTORIS, HIPERTENSION ARTERIAL Y ARRITMIAS CARDIACAS: TRATAMIENTO MODERNO

Auspiciado por:

División de Educación Médica Continuada
Escuela de Medicina
Universidad de Puerto Rico

CATEGORIA I — 5 HORAS-CREDITO

Lugar: Hotel Palace (Salón Andorra)

Hora: 8:00 A.M. a 2:00 P.M.

Fecha: Domingo 12 de agosto de 1984

Para información adicional favor de comunicarse con los teléfonos:
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DIVISION ENDOCRINOLOGIA Y METABOLISMO

DEPARTAMENTO DE MEDICINA
ESCUELA DE MEDICINA
UNIVERSIDAD DE PUERTO RICO

PRESENTA

NUEVOS AVANCES EN EL TRATAMIENTO DE LA DIABETES MELLITUS NO INSULINO DEPENDIENTE

Auspiciado por:

División de Educación Médica Continuada
Escuela de Medicina
Universidad de Puerto Rico

CATEGORIA I 4 1/2 HORAS-CREDITOS

FACULTAD

Francisco Aguiló, Jr., M.D.
Rafael A. Camerini Dávalos, M.D.
Harold Lebovitz, M.D.

TEMAS

Enfoque del Paciente Diabético de Clínica, Categorización y Control: ¿Por qué?

Reversión de la Microangiopatía Diabética Temprana Inducida por Agentes Hipoglicémicos Orales

Mecanismos de Acción de Glipizide (Sulfonilurea de Segunda Generación)

Problemas Prácticos en el Manejo del Paciente no Insulino Dependiente

FECHA: domingo, 19 de agosto de 1984

HORA: 8:00 A.M. a 2:00 P.M.

LUGAR: Hotel Caribe Hilton

COSTO DE MATRICULA: \$10.00

PARA INSCRIPCION LLAMAR:
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University of Miami
Miami, Florida

DIVISION OF CONTINUING MEDICAL EDUCATION

Clinical Pediatric Cardiac Electrophysiology sponsored by the University of Miami, School of Medicine will be held **November 9-11, 1984** at the Eden Roc Hotel, Miami Beach, Florida, Course Director: Grace S. Wolff, M.D., Course Hours: 12.0. For information contact: Division of CME D23-3, P.O. Box 016960, Miami, Florida 33101 Tel: (305) 547-6716.

Advances in Spinal Surgery VI sponsored by the University of Miami School of Medicine will be held **November 25-30, 1984** at the Sheraton Bal Harbour, Bal Harbour, Florida. Course Directors: Mark D. Brown, M.D., Ph.D., Frank J. Eismont, M.D., Barth A. Green, M.D. Course Hours: 33 AMA, AANS/CNS. For information contact: Division of CME D23-3, P.O. Box 016960, Miami, Florida 33101 Tel: (305) 547-6716.

Emergencies in Internal Medicine VII sponsored by the University of Miami School of Medicine will be held **December 12-18, 1984**, at the Frenchman's Reef Beach Resort, St. Thomas, Virgin Islands. Course Director: Laurence B. Gardner, M.D. Course Hour: 35, For information contact: Division of CME D23-3, P.O. Box 016960, Miami, Florida 33101, Tel. (305) 547-6716.

The American Academy of Clinical Anesthesiologists

The American Academy of Clinical Anesthesiologists **Fall Seminar October 24-27, 1984**, Grove Park Inn, Asheville NC 28804, Write to AACA, Knoxville TN 37939-1691, Tel. (615) 588-6279.

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The Nuclear Medicine Section of The Department of Radiology of the University of California, San Diego School of Medicine will present a continuing medical education seminar: **Nuclear Imaging, with Emphasis on Physics**. The Course will feature topics in cardiac and

abdominal nuclear radiology and is designed to assist residents in physics board review. The Course will be offered **January 20-30, 1985**, at the Holiday Inn at the Embarcadero in San Diego, California. The Program Director is William L. Ashburn, M.D.

The tuition fee for the Course is \$400.00 or \$350.00 for residents, fellows and technologists.

For more information, please contact Dawne Ryals, Ryals and Associates, Conference Managers, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel. (214) 659-9590.

The Ultrasound Section of The Department of Radiology of the University of California, San Diego School of Medicine will present a continuing medical education seminar: **San Diego Abdominal and Obstetrical Imaging Symposium Update**. The Course will feature topics in Ultrasonography, Computed Tomography and Interventional Radiology and will be offered **February 11-15, 1985** at the new Hotel Intercontinental in San Diego, California. The Program Director is George R. Leopold, M.D.

The tuition fee for the Course is \$425.00 or \$300.00 for residents, fellows and technologists.

For more information, please contact Dawne Ryals, Ryals and Associates, Conference Managers, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel. (214) 659-9590.

The Department of Radiology of the University of California, San Diego School of Medicine will present a continuing medical education seminar: **Fifth Annual Residents' Radiology Review Course**, including cardiovascular radiology, **April 29-May 3, 1985** at the Town and Country Hotel in San Diego, California. The Course is designed to assist residents or practicing radiologists in a general review. The Program Chairman is Robert N. Berk, M.D. and the Program Director is Folke J. Brahme, M.D.

The tuition fee for the Course is \$370.00.

For more information, please contact Dawne Ryals, Ryals and Associates, Conference Managers, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel. (214) 659-9590.

The Department of Radiology of the University of California, San Diego School of Medicine will present a continuing medical education seminar: **Eleventh Annual San Diego Post-graduate Radiology Course, October 28-November 1, 1985** at the Hotel del Coronado in San Diego, California. The Course topics will include MRI, Ultrasonography, Computed Tomography, and Interventional, as well as general radiology review topics. The Program Chairman is Robert N. Berk, M.D.

The tuition fee for the Course is \$425.00.

For more information, please contact Dawne Ryals, Ryals and Associates, Conference Managers, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel. (214) 659-9590.

The Department of Radiology of the University of California, San Diego School of Medicine will present a continuing medical education seminar: **Radiology of the Abdomen, December 2-6, 1985** at the Hotel Intercontinental in San Diego, California. The Course topics will include MRI, Ultrasonography, Computed Tomography, and Interventional. The Program Chairman is Robert N. Berk, M.D. and the Program Director is Eric vanSonnenberg, M.D.

The tuition fee for the Course is \$400.00.

For more information, please contact Dawne Ryals, Ryals and Associates, Conference Managers, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel (214) 659-9590.



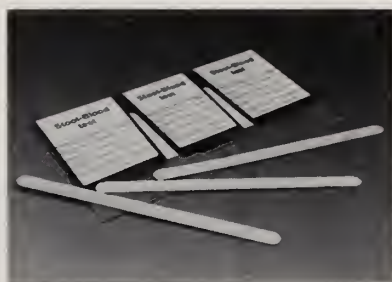
A Seminar: **Diagnosis of Diseases of the Chest** will be offered by the Great Teachers Foundation, **March 29-31, 1985** at the Four Seasons Mandalay, Dallas, Texas.

The Course will be accredited for 22 hours Category I AMA certification. The fee will be \$325.00 and \$225.00 for residents, fellows and technologists.

For more information, please contact Dawne Ryals, Ryals and Associates, P.O. Box 610203, DFW Airport, TX 75261-0203. Tel (214) 659-9590.

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Other tests for colorectal cancer you should talk to your doctor about: digital rectal exam (after age 40); the procto test (after age 50). It is important to report any personal or family history of intestinal polyps or ulcerative colitis, and any change in your bowel habits, which could be a cancer warning signal.

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CYTOMEGALOVIRUS INFECTION AND BLOOD TRANSFUSION

The following report, prepared by the AABB Committee on Transfusion Transmitted Diseases (TTD), chaired by Joseph R. Bove, MD, was recently approved by the Board of Directors. The Committee on Pediatric Hemotherapy and several outside consultants with a special interest in pediatric infectious diseases provided input to the TTD Committee.

As is clear from our statement, the risk of significant illness from transfusion transmitted cytomegalovirus (CMV) varies with the recipient population. In addition, current evidence—much published only in abstract form—suggests that the risk for similar recipient groups varies in different parts of the country. The data that form the basis of our recommendations are not entirely satisfactory, but provide enough documentation to support the positions we have taken. These recommendations may need to be strengthened or weakened depending upon the outcome of future studies or the availability of new approaches such as CMV vaccine or hyperimmune globulin. These facts notwithstanding, we believe that the risk is great enough in some groups and in some areas to suggest that selected blood banks and transfusion services need to act appropriately.

It is well accepted that certain patients may develop CMV infection as manifested by seroconversion, a rise in antibody titer, or shedding of virus following blood transfusion.¹ Because transfusion-transmitted CMV infection is usually associated with undetectable or mild disease, prevention of infection should be directed toward those few clinical situations where significant morbidity and mortality have been seen.

- 1) Infection in immunocompetent patients is manifested by subclinical or mild clinical disease without apparent significant sequelae. There is no need to take special precautions for these patients.
- 2) The limited evidence suggesting a risk in infants who either weigh more than 1250 gms at birth, or who have a seropositive (anti-CMV antibody present) mother is insufficient to justify special products for these patients at this time.

- 3) Infants who are born of seronegative mothers and who weigh less than 1250 gms at birth may be at risk of morbidity and mortality from transfusion-transmitted CMV.^{2, 3} Preliminary reports suggest that such morbidity and mortality may be found in some, but not all, parts of the country^{4 5 6} perhaps related to the relative frequency of seropositivity of mothers and blood donors in a given geographic area. Special products are unnecessary in areas where an increased risk of transfusion-transmitted CMV morbidity and mortality has been sought and not found. In areas where risk is high or unknown, it is prudent to provide products with a reduced risk of transmission of CMV infection of infants who weigh less than 1250 gms and were born to CMV seronegative mothers.

Is important to re-emphasize that a risk of significant CMV disease has not been shown in fullterm neonates. There has even been a suggestion of increased risk when CMV seronegative blood is given to premature infants of seropositive mothers.⁷ This may be the result of decline in passively acquired maternal antibody when blood loss is replaced by CMV seronegative products.

- 4) Since the risk of serious congenital CMV infection seems to be greater with primary infection in the mother,⁸ it is desirable to provide low-risk products for elective transfusion of seronegative pregnant women.
- 5) While the transplantation of a CMV seropositive kidney to a CMV seronegative recipient can be associated with high morbidity and mortality,⁹ there is a suggestion that no increased morbidity and mortality is associated with transfusion-transmitted CMV infection in these patients. We make no recommendation in this area.
- 6) CMV infections following prophylactic granulocyte transfusions have been associated with morbidity and mortality in bone marrow recipients.¹⁰ This should be prevented by use of granulocytes from CMV negative donors. We are unaware of data suggesting that other products carry significant risks of CMV associated morbidity and mortality other than discussed above.

Several approaches to the provision of blood with a lower risk of transmission of CMV infection have been described. The one best supported by clinical data is the use of blood components from seronegative donors, defined as an antibody titer of less than 1:8 (IgG antibody) in an indirect hemagglutination assay.² Several relatively simple and inexpensive tests have been developed.¹¹ Several of these are highly reproducible and should provide blood of comparable safety where seronegative products are indicated. There is a preliminary suggestion that tests to detect IgM anti-CMV may be of special interest.⁴

Deglycerolized Red Blood Cells, even from seropositive donors, appear to be as safe as seronegative blood.^{12, 13} This product should be equally effective for patients at risk of significant CMV disease. Although not proven, Washed Red Blood Cells may be an acceptable alternative. Clinical trials are underway to test this hypothesis.

Committee: Joseph R. Bove, MD, chairman, Harold A. Oberman, MD, vice chairman, George Grady, MD, Alfred Grindon, MD, Paul Holland, MD, James Shorey, MD, Richard Wasserman, MD.

Consultants: Naomi Luban, MD, Jay Menitove, MD, Ronald Sacher, MD, Gerald Sandler, MD.

References

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INEXPENSIVE HEPATITIS B VACCINE EXPECTED IN TWO TO FOUR YEARS

Scientists in California and New York announced recently that they have isolated a small portion of the hepatitis B virus that can be used to produce a safe and inexpensive synthetic vaccine, according to the *Wall Street Journal* and *Science* magazine. The vaccine currently being produced by Merck, Sharp and Dohme is considered too expensive for large-scale use, the *Journal* reported.

Studies from the New York Blood Center and the California Institute of Technology in Pasadena, isolated two antigens from the virus containing a common chain of molecules that "seemed to be part of the antigen that provoked the immune response." The synthetic molecular chain produced by a new method is being tested on rabbits. "The animal antibodies reacted with the intact

virus and related particles to such an extent we have been able to use them to detect hepatitis B virus in human blood serum at a dilution of one millionfold," reported the New York Blood Center group.

The next step is to discover if the synthetic peptide causes chimpanzees to produce antibodies against the virus, and then immunize the chimps against the disease. If tests are successful, a cheaper vaccine could be available by 1987.



AMERICAN COLLEGE OF
EMERGENCY PHYSICIANS

ACCURACY OF A BREATH ALCOHOL ANALYZER

"A significant percentage of evening patients in emergency departments have been drinking," according to a study appearing in *Annals of Emergency Medicine*. Similar studies have found that 42% of the patients in an emergency department in the evening have been drinking, and 30% of the patients have consumed a significant amount of alcohol. *Annals* is the monthly clinical journal published by the American College of Emergency Physicians (ACEP).

In a series of patients with concussions in the emergency department, authors of the *Annals* study reported 40% had been drinking, and blood alcohol levels in 36% were greater than 0.10, the legal drunk limit in most states. Thirty percent of teenage drivers involved in automobile accidents had been drinking. In addition to alcohol intoxication, many patients had associated problems, such as head injury, multiple trauma, disturbances, drug overdose, behavioral emergencies or coma.

Kenneth A. Gibb, MD, author of the study, and his colleagues conducted the research to determine the accuracy of a hand-held breath alcohol analyzer in rapidly assessing emergency patients with suspected alcohol intoxication. The patients were divided into cooperative and uncooperative groups to determine whether the level of cooperation affected test reliability.

"A rapid and dependable method of measuring blood alcohol levels helps in the evaluation and management of patients with altered mental status, which often is attributed erroneously to alcohol," explained Dr. Gibb.

According to Dr. Gibb, cooperativeness was determined subjectively by the examining physician, depending on whether the subject understood and followed instructions.

"Results of our study demonstrated a high correlation between alcohol levels measured by the hand-held breath analyzed device and blood alcohol levels in both cooperative and uncooperative patients," reports Dr. Gibb.

Hand-held breath alcohol analyzers are used primarily for detection of intoxicated automobile drivers. These breath alcohol analyzers also have been used to detect use of alcohol in drug and alcohol treatment programs, and in pre-employment screening programs.

AMERICAN COLLEGE OF PHYSICIANS



ACP REVIEWS RADIOLOGIC METHODS TO EVALUATE BONE MINERAL CONTENT

A recommendation on the use of radiologic methods to evaluate bone mineral content in the diagnosis of metabolic bone diseases has been released by the Clinical Efficacy Assessment Project (CEAP) of the American College of Physicians (ACP).

The recommendation examines the safety, efficacy and cost of several noninvasive procedures of determining bone mineral content: radiogrammetry, photodensitometry, single energy photon absorptiometry, dual energy photon absorptiometry, computed tomography (CT), and neutron activation analysis. The various methods are evaluated by the College for precision, reliability and radiation exposure. A comparative table accompanies the recommendation, which is published in full in the June 1984 *Annals of Internal Medicine*.

Because these non-invasive techniques allow for quantitative measurements of bone mass, the College found them to be more appropriate for use with osteoporosis (which causes a decrease in bone mass) than in conditions that cause a qualitative bone defect, such as osteomalacia, hyperparathyroidism (which may result in pain and tenderness of the bones and spontaneous fractures), and renal osteodystrophy.

In assessing radiologic methods to evaluate bone mineral content for their value in diagnosing specific bone diseases, the ACP found them to be more useful in following the course of a disease process, monitoring drug complications such as bone mineral loss due to steroid therapy, or assessing the effect of treatment.



ASIM ASKS DHHS TO EVALUATE EFFECTS OF DRGs ON PATIENT CARE

Concerned about the apparent absence of any coordinated and much-needed effort to evaluate the effects on patients care of Medicare's new prospective hospital payment system based on diagnosis-related groups (DRGs), the American Society of Internal Medicine (ASIM) wrote Margaret M. Heckler, Secretary of the Department of Health and Human Services (DHHS), to suggest a series of activities to ensure that policymakers will have data necessary to

decide whether to continue or modify the program. Such information is also vitally important to making future determinations about extending such a payment system to include physicians' in-hospital services. In addition, the Society is attempting to gather data on its own on the effects of DRGs on patient care by surveying internists nationwide.

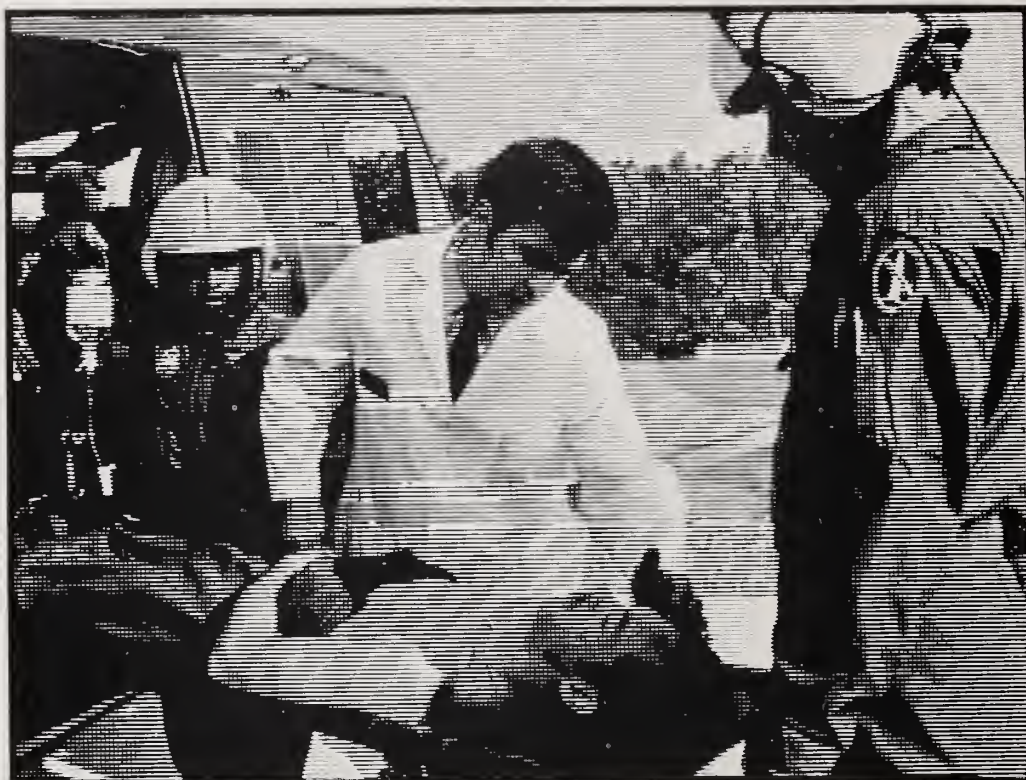
Specifically, ASIM asked DHHS to:

- Collect national data on mortality and morbidity rates for Medicare patients, including a comparison of such rates before and after implementation of the DRG-based system;
- Conduct periodical, confidential surveys of physicians, hospitals and patients to elicit their evaluations of the system's effects on patient care;
- Compile and report aggregate peer review organization (PRO) data to help identify trends on the number of hospital readmissions caused by limiting care or underutilizing services;
- Consider developing research studies to compare experiences of states operating under the national DRG-based system with those operating under waivers from it;
- Appoint a multi-departmental task force of representatives from several agencies to develop a plan to obtain, coordinate and report to Congress and the public all appropriate information on the system's impact on patient care; and
- Advise ASIM about any federal activities similar to or different than the above that DHHS is planning or has implemented in this regard.

"During the debate preceding passage of the DRG legislation, ASIM and other medical groups repeatedly urged Congress to carefully examine the potential adverse effects on patient care (such as underprovision of services, skimping on care to maximize profits, artificially inflating diagnoses to get higher payment, known as 'DRG creep,' and providing lower quality care to Medicare beneficiaries) before launching the program nationwide," wrote ASIM President John D. Abrams, MD, of Albuquerque. "Now that the system is being implemented across the country, ASIM is concerned about the apparent lack of any coordinated effort on a nationwide basis to document these possible adverse effects on the quality of patient care."

Because of the Society's growing concerns, ASIM has initiated its own attempt to document the effects of DRGs—both positive and negative—on patient care by asking internists across the country to complete and return the attached survey that was distributed in the March issue of *The Internist* and offered by request in the Society's May newsletter. Members receiving it were also asked to pass copies of it along to other internists. Responses will be tabulated as received and any identifiable trends will be reported to Congress and DHHS, among others, periodically.

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STUDY FINDS POTENTIAL MARKER FOR AIDS

A study reported in the June 8 issue of JAMA provides evidence of a surrogate marker for acquired immune deficiency syndrome (AIDS).

Researchers Susan Zolla-Pazner, PhD, of the Veterans Administration Medical Center, New York, and colleagues found that elevated levels of B₂ microglobulin (B₂M) characterized patients with confirmed and suspected AIDS. "In addition, the data suggest that quantitation of B₂M serves as a valuable component in a screen for persons in groups at high risk for AIDS," they say.

In the study, serum samples from 24 patients with AIDS and from 15 patients with an early or milder form of the disease (suspected AIDS) were found to contain elevated levels of B₂M. The researchers then studied 40 asymptomatic homosexual men to determine whether quantities of B₂M and other immunologic variables could be used to identify members of high-risk groups who were likely to develop AIDS. They found that after 20 to 26 months of follow-up, two of these men had AIDS and four had suspected AIDS. All six had elevated serum B₂M levels and other immunologic abnormalities when they entered the study, the researchers say.

The researchers report that only one man had elevated levels of B₂M with no other immune abnormalities, and neither he nor any of the other 33 men in the group of 40 developed AIDS. They add that the B₂M test, like other tests used in studies of patients with AIDS, is not specific for the disease. Patients with B-cell malignancies, autoimmune diseases, diseases associated with chronic inflammation, or acute viral infections may also have elevated levels of B₂M.

Although the specificity and sensitivity of the B₂M test is impossible to compute, the researchers conclude that it seems to be a useful marker for early stages of AIDS when used in conjunction with other laboratory tests. They add, "While it is premature, on the basis of these data, to describe B₂M quantitation as a test that is adequate for the screening of healthy populations for AIDS, it may be a useful method for recognizing persons with possible asymptomatic AIDS who are members of populations known to be at high risk for AIDS."

In a related JAMA Medical News article, Charles Marwick reports that it remains to be determined

whether French and American investigators have isolated the same virus as the cause for AIDS. Robert C. Gallo, MD, of the National Cancer Institute denies any controversy between the two groups, and adds, "If the agents turn out to be the same, I will certainly say so in a collaborative report with them." Gallo says the most immediate potential application of the findings is the possibility of testing donor blood before transfusion. Marwick reports other long-range benefits of the discovery include treatment for patients with AIDS and possible development of a vaccine.

DRUG COMBINATION PREVENTS POSTSURGICAL THROMBOSIS

Researchers participating in a multicenter trial have determined that one drug combination is especially effective in preventing deep vein thrombosis (DVT) in patients undergoing elective surgery. Their findings are reported in the June 8 issue of JAMA.

According to the principal investigator, Arthur A. Sasahara, MD, of the Veterans Administration Medical Centers in West Roxbury and Brockton, Massachusetts, and colleagues from 15 other centers, the risk of DVT of the lower extremities is relatively high for patients aged 40 years or older who undergo major surgery. The death rate for this group from postsurgical pulmonary embolism is nearly 1 percent; it is about 0.2 percent for all patients undergoing surgery. Pulmonary embolism from DVTs accounts for 150,000 deaths each year in the United States, the researchers say.

To test the effectiveness of various drug doses in preventing DVT, the study included 880 patients, all aged 40 years and older, who were randomized into five treatment groups including four receiving varying amounts of dihydroergotamine mesylate and/or heparin sodium and one group receiving placebo. Treatment was started two hours before surgery and continued twice daily for five to seven days. Rates of DVT ranged from 9.4 percent, to 24.4 percent with the placebo. The drug combination of dihydroergotamine mesylate, 0.5 mg, plus heparin sodium, 5,000 IU, was shown to be significantly superior to other treatments.

The researchers note that although the administration of heparin sodium has been to be effective in preventing DVT, the fear of causing increased bleeding has discouraged its widespread use. More recent clinical trials have shown that heparin in combination with dihydroergotamine mesylate (which tends to constrict certain blood vessels) is more effective than the same dose of heparin alone.

In this multicenter trial, adverse drug experiences did not differ significantly between groups, and the researchers report a low incidence of bleeding or hematoma. There was one death that may have been drug related, they say, which demonstrates the need for terminating administration of dihydroergotamine in any patient who experiences sepsis, low blood pressure or heart attack.

In a related editorial, Jack Hirsh, MD, of the McMaster University in Hamilton, Ontario, says that primary prophylaxis, as used in this study, is more effective and less expensive than early detection and treatment of subclinical venous thrombosis. He adds, "This large well-conducted study provides the clinician with useful information. It demonstrates once again that low-dose heparin does not produce clinically significant bleeding when this complication is assessed using a double-blind trial design." Hirsh says heparin is contraindicated in some types of surgery and that new forms of the drug, as well as other therapies, are being tested to determine the safest prophylaxis for DVT.

DEDICATED SUN WORSHIPERS DISDAIN SUNSCREENS

Most sun worshipers refuse to use sunscreens even when carefully informed of the hazards of sun exposure and of the benefits that sunscreens provide, according to a new study reported in the June 1984 *Archives of Dermatology*.

Researchers Esther Y. Johnson and Donald P. Lookingbill, MD, of the Pennsylvania State University College of Medicine in Hershey, surveyed 489 patients during the summer months to evaluate their sun-exposure habits and beliefs. Among their findings: 71 percent had one or more hours of sun exposure on at least one day per week; men had more exposure than women; subjects under 30 spent more time in the sun than those over 30. Most important, only 41 percent used sunscreens, typically in the belief they would promote tanning. Subjects were given samples of appropriate sunscreens and informational pamphlets.

Some 340 patients were contacted by telephone four weeks later for follow-up evaluation. Virtually all demonstrated better knowledge of sun-exposure risks and the need for sun protection, but virtually none demonstrated improved use of sunscreens.

"We were able to significantly improve our patients' accurate knowledge concerning sun-protective factor (a SPF, formula for measuring protective values of sunscreens) and the risks of skin cancer and wrinkling with sun exposure, presumably the result of the subjects reading the informational pamphlet that was provided," the researchers say.

"Improvement in sunscreen use in sun-exposed nonusers, however, was poor; only one-third of this group used the free sample and only five percent subsequently bought a sunscreen," they say.

Long noted as a major cause of skin cancer, sun exposure also can cause wrinkling and lead to adverse changes in skin collagen, the protein substance of the write fibers of the skin, and elastic fibers.

"There is a need to educate people as to the appropriate choice and use of sunscreens," the researchers say. "Since sunscreens are now available in a wide range of SPFs (an SPF of 15 is considered most effective), most of which are indicated on the product label, patients need to be fully informed."

Patients also need to be informed of the difference between sunscreens and tanning lotions, they add. Many mistakenly think sunscreens promote tanning while others mistakenly think lotions prevent sun burning.

In any event, behavior will be difficult to change because people like the looks of a tan, the researchers say: 72 percent believe a suntan looks attractive; and 78 percent believe it looks healthy. "Any habit that has such strong positive reinforcement is difficult to modify with persuasion, including medical evidence," they conclude.

NEW BOOK ON MALNUTRITION IN THE AMERICAS AVAILABLE

Proceedings of the Western Hemisphere Nutrition Congress VII are now available. Published by Alan R. Liss, Inc., New York, *Malnutrition: Determinants and Consequences* was edited by Philip L. White, ScD, and Nancy Selvey, RD, of the American Medical Association.

The Congress, held in Miami Beach in August 1983, had multiple sponsors, speakers from all parts of the Americas and attendees from 35 countries.

Malnutrition: Determinants and Consequences considers the problem of malnutrition and food scarcity as a regional concern, surveying conditions in North America, Latin America and the Caribbean. Specific factors contributing to hunger and their consequences are discussed: the effects of malnutrition on mothers and nursing infants, urbanization and demographic change, nutritional factors affecting immune responses, individual food intake, attempts to increase agricultural productivity, and implications for health care. An open panel discussion presents case studies detailing conditions in several Caribbean communities and makes recommendations for approaches to the problems on a local level. The book closes with a survey of strategies for addressing the hunger problem on a regional basis and emphasizes the need to bring policy makers up to date with current scientific insight.

The book will be of interest to nutritionists, obstetricians, gynecologists, pediatricians, public health professionals, government planners involved with agricultural and urban development, and community caseworkers.



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VA PSYCHIATRISTS SHOULD HAVE WARNED VICTIM OF PATIENT'S DANGEROUSNESS

There was no clear error in a trial court's finding that psychiatrists' failure to warn a woman about the man she was living with was the proximate cause of her death, a federal appellate court in California ruled.

The man threatened and apparently attempted to rape the woman's mother, and the woman discussed with police the possibility of his receiving psychiatric treatment. He volunteered to undergo a psychiatric examination at a Veterans Administration hospital.

A policeman advised the head of psychiatric services of the man's prior criminal record, recent history of obscene telephone calls, and malicious damage. The treating physician was not given this information but learned in a subsequent interview that the man had been imprisoned for raping his former wife. He refused to state where he had received prior psychiatric treatment.

The physician recommended voluntary hospitalization, but the man refused. The woman and her minor child moved out of the man's apartment because of warnings. However, the woman went back to pick up some possessions, at which time the man attacked and murdered her.

The child brought an action for wrongful death under the Federal Tort Claims Act, alleging that negligence of the psychiatrists proximately resulted in her mother's death. The trial court decided in the child's favor, finding malpractice for failure to record and transmit information from the police, failure to obtain the man's past medical records, and failure to adequately warn the woman.

On appeal, the government claimed, among other things, that no duty was owed to the woman because the man was an outpatient and the woman was not a foreseeable victim of his violent tendencies. The government also contended that the alleged negligence was not the proximate cause of the woman's death. The court said that no policy regarding veteran medical records prevented the physicians from obtaining the man's records, and nothing prevented them from recording and communicating the information given by the police. The court pointed out that

the man's previous history indicated that his violence would be directed against the woman, as his psychological profile indicated that his violence was likely to be directed against women very close to him.

The court agreed with the trial court that the physicians had been negligent in failing to obtain the man's prior medical history. The court also agreed that the physician's warnings to the woman were totally unspecific and inadequate under the circumstances. The court said that the trial court's finding that the information from the man's prior records, properly used, would have prevented the murder was not clearly erroneous. The court affirmed the lower court's decision. —*Jablonski v. U.S.*, 712 F. 2d 391 (C.A.9, Cal., June 14, 1983; as amended, Aug. 8, 1983).

PHYSICIANS LIABLE FOR DISCHARGING MENTAL PATIENT

Evidence sustained a finding that a hospital and physicians failed to exercise a reasonable degree of skill, knowledge and care to determine whether a psychiatric patient should be discharged, a federal trial court in Kansas ruled.

The patient had been committed to a state hospital after telling his grandparents that he had planned to "knocked them off and take the Toyota." The probate court ruled that he was a mentally ill person, potentially dangerous to himself and others. Approximately four months later, the clinical director of the hospital suggested that the patient be discharged to save the money it would cost for a planned transfer to another hospital. Shortly after his discharge, the patient shot and killed his mother and brother.

The patient's father brought a wrongful death action against five physicians who participated in the decision to discharge the patient from the hospital. A jury awarded the father and two sons \$92,300.

The physicians and hospital moved for a new trial. They contended that they should have been permitted to present a defense of contributory negligence at the trial. They said that it was his family that made the patient sick in the first place. The court said that if, in fact, the patient's conditions was caused or aggravated by the family, it would seem all the more reason not to discharge the patient to their custody and care.

The physicians also contended that the father's expert witness should not have been allowed to testify because he was unqualified. The witness was a clinical psychologist who had been on the staff of another state hospital, with duties similar to those of the team on the ward where the

patient stayed. The physicians contended that the psychologist was not qualified to testify because he had no medical training, was licensed by a different board, and therefore could not give an opinion as to the usual and approved practice or care or lack thereof exercised by the physicians. The court pointed out that the decisions in question in this case were psychological and not medical. The expert for the physicians, who was a psychiatrist, and the clinical director, also a psychiatrist, agreed that there was one body of knowledge common to psychology and psychiatry. The court found no error in allowing his testimony.

The psychologist testified that he would not have discharged the patient. He felt that the patient was clearly a risk for a lethal act shortly after discharge, either toward himself or a close friend or relative. He criticized the way in which the patient was discharged. He and a psychiatrist indicated standards of care that the jury could conclude should have been followed. The court said that their testimony indicated standards of care that the jury could conclude should have been followed and that ample evidence led to the conclusion that such standards were not met. The court denied the motion for a new trial. —*Durflinger v. Artiles*, 563 F. Supp. 322 (D.C., Kan., June 12, 1981).

PHYSICIANS NOT LIABLE FOR ALLEGED KILLING BY PATIENT

A mother whose son was killed by a patient on a two-day pass from a state mental hospital had no cause of action against the treating physicians, the Missouri Supreme Court ruled.

The mother filed suit against the state and various physicians and officials. She charged that the patient was involuntarily committed to the state hospital and that he was dangerous and had severe mental illness. The complain alleged that the physicians released him on a two-day pass contrary to law and did not take proper steps to return him to custody by notifying the sheriff. The patient allegedly killed her son on May 4, 1978, by shooting him in the head 11 times with a rifle.

A trial court dismissed the case against the state officials and physicians, and the Supreme Court affirmed. The physicians did not owe a duty to the general public in deciding which involuntary patients should be released on a pass or in obtaining the return of patients temporarily released.

The court distinguished cases holding that a psychotherapist had a duty to warn an identifiable person threatened by a patient. The court said that treating physicians should not have to function under the threat of civil liability to members of the general public when making decisions about passes and releases. —*Sherrill v. Wilson*, 653 S.W. 2d 661 (Mo.Sup.Ct., June 30, 1983).

CLINIC DOES NOT HAVE TO PROVIDE SPECIAL CARE FOR PATIENT IN COMA AFTER A SUICIDE ATTEMPT

A hospital psychiatric clinic did not breach any duty to a guardian of a patient by removing 24 hour nursing care where the patient's treatment was being provided gratuitously and the guardian had the option to remove the patient from the clinic, a federal trial court in New York ruled.

The patient was admitted to the clinic after she tried to commit suicide. Two days later, she was found hanging by her shoelace in her room. After the second suicide attempt, the patient was brain damaged, in a coma, and fed by a stomach tube.

The hospital agreed voluntarily to provide medical care and treatment for the patient, and the patient's guardian agreed to care by a neurologist. She received 24-hour, one-to-one nursing care at hospital expense for more than six months. At that time, the neurologist discussed transfer of the patient to a semiprivate room with a constant companion. The guardian rejected the transfer and chose to provide one-to-one, 24 hour nursing care at her own expense.

The guardian brought a malpractice action against the clinic and sought an injunction to compel restoration of 24-hour care or an amount equal to the cost of the companion care thought to be medically necessary by the clinic. The neurologist, in an affidavit, stated that he felt that the care in a semiprivate room was reasonable at the time. The patient's family physician disagreed, stating in an affidavit that round-the-clock nursing care was indicated.

The court said that in order for the guardian to establish the right to the injunction sought there must be a duty by the clinic to the patient that was being violated. There were a number of theoretically possible alternatives for the patient, including discharge and replacement of the neurologist and removal of the patient to another facility. The court said that the guardian could not fail to exercise these options and also assert that there would be irreparable injury unless the court compelled the clinic to provide more care than the neurologist felt necessary. The court denied the application for an injunction. —*Katepoo v. New York Hospital*, 562 F. Supp. 875 (D.C., N.Y., May 6, 1983).

PHYSICIANS WHO WITHDREW LIFE-SUSTAINING TREATMENT CANNOT BE CHARGED WITH MURDER

The complaint against two physicians charging them with murder because they withheld life sustaining treatment was properly dismissed, a California appellate court ruled.

The patient underwent surgery for the closure of an ileostomy. In the recovery room after the surgery, the

patient suffered cardio-respiratory arrest. He was revived and placed on life-support equipment. Within three days, physicians decided that the patient had suffered severe brain damage that left him in a vegetative state and that was likely permanent. The surgeon and attending physicians communicated to the family that the prognosis for recovery was extremely poor. The family met, and drafted a request to the hospital for the removal of the patient from all life-sustaining machines. After the equipment was removed, the patient continued to breathe, but showed no signs of improvement. Two days later, after consulting with the family, the physicians ordered the removal of the intravenous tubes that provided nourishment and hydration. The patient received nursing care until his death.

The patient's two physicians were charged with murder and conspiracy to commit murder. The magistrate dismissed the complaint. A superior court judge ordered reinstatement of the complaint based on the conclusion that the physicians' conduct, which shortened the patient's life, constituted murder. The appellate court reversed the superior court's order and found that the physicians' conduct was not unlawful and that they had not failed to perform a legal duty.

The court stated that the physicians' conduct had to be evaluated on the basis of principles other than the California accidental and justifiable homicide statutes. The court noted that California had adopted the Natural Death Act, which allowed adults to execute a directive for withholding or withdrawing of life-sustaining procedures if they later suffer a terminal condition. The court stated that this did not purport to be the exclusive means by which such decisions can be made. Further, the court stated that a diagnosis of brain death was not a condition precedent to cessation of this treatment.

"As a predicate to our analysis of whether the petitioners' conduct amounted to an 'unlawful killing', we conclude that the cessation of 'heroic' life support measures is not an affirmative act but rather a withdrawal or omission of further treatment.

"Even though these life support devices are, to a degree, 'self-propelled', each pulsation of the respirator or each drop of fluid introduced into the patient's body by intravenous feeding devices is comparable to a manually administered injection or item of medication. Hence 'disconnecting' of the mechanical devices is comparable to withholding the manually administered injection or medication.

"Further we view the use of an intravenous administration of nourishment and fluid, under the circumstances, as being the same as the use of the respirator or other form of life support equipment," the court said.

The court resolved the issue of whether or not the physicians had a duty to continue to provide life-sustaining treatment in the negative. Once life-sustaining treatment becomes futile in the opinion of qualified medical personnel, there is no duty to continue its use. Whether the procedures have become futile will depend on the facts of each case, but the court suggested that the focal point of this determination would be the chances of return to cognitive and sapient life. How long the treatment will extend life and under what conditions also is

relevant.

The court stated that the authorization of the removal of life-sustaining treatment did not require legal proceeding or judicial approval. The court stated that, although legislative action in this area would be useful, none existed. In this case, the court noted that the family agreed to withdraw treatment and no contrary opinion of the patient was made known.—*Barber v. Superior Court of the State of California for the County of Los Angeles*, 195 Cal.Rptr. 484 (Cal.Ct. of App., Oct. 12, 1983)

COURT REVERSES ORDER TO REMOVE FEEDING TUBE

A trial court's order permitting removal of the nasogastric tube from an 84-year-old patient who was not brain dead should be reversed, a New Jersey appellate court ruled.

The patient suffered from organic brain syndrome and other physical problems. She was fed through a nasogastric tube. Her nephew was appointed guardian in 1979, and later a trial court authorized him to remove the nasogastric tube. At the hearing her physician testified that the patient was not brain dead, not comatose, and not in a chronic vegetative state. Severe contractions of her lower legs kept her in a semi-fetal position. She did not respond to verbal stimuli but followed movements with her eyes.

On appeal, the trial court's order was reversed. The court balanced the minor bodily invasion from the nasogastric tube with death from dehydration and starvation. The state's interest in preserving her life outweighed the patient's privacy interest, the court said. The right to terminate life-sustaining treatment based on a guardian's judgment should be limited to the incurable and terminally ill who are brain dead, irreversibly comatose or vegetative, and who would gain no medical benefit from continued treatment, the court concluded.

Under the circumstances, discontinuance of the nasogastric tube could not be permitted on a theory of right to privacy or on any other basis, the court said.—*In the Matter of Conroy*, 464 A.2d 303 (N.J. Super. Ct., App. Div., July 8, 1983)

WITHDRAWAL OF LIFE SUPPORT AUTHORIZED

Once a patient was determined to be brain dead, his guardian could authorize the health care provider to withdraw the life-support system, a California appellate court ruled.

A 19-day-old infant with a seizure disorder was admitted to the emergency room of a local hospital and later transferred to a university medical center. Tests showed increased intracranial pressure, and the infant was placed on a respirator. His condition deteriorated significantly, and by the end of the week, he failed to respond to any stimulation. Attending physicians concluded that he was

brain dead. They recommended removing the respirator but, following hospital policy, they deferred to the parent's wishes.

The parents, who had been arrested and charged with child abuse, withheld consent to withdraw the respirator. A guardian was appointed for the infant and, after a hearing, the court directed the guardian to consent to withdrawal of the life-support system. The parents moved for an order preventing removal of the life-support system.

The court said that the evidence supported a finding that the infant had suffered brain death. Once brain death was determined, no criminal or civil liability will result from disconnecting the life-support devices. The court recognized that parents have the right to participate in the decision to remove the life-support system. Where the parents were unavailable by their actions, the guardian could make the decision, the court said.

The court denied the motion to prohibit removal of the life-support system.—*Doroty v. Superior Court of San Bernardino County*, 193 Cal.Rptr. 288 (Cal. Ct. of App., July 21, 1983)

NO WRONGFUL DEATH SUIT FOR UNBORN VIABLE CHILD

The father of a viable unborn child may sue for expenses and actual loss of services for the death of the unborn child although the child's estate had no wrongful death claim, the Iowa Supreme Court ruled.

The father brought the suit as a result of a traffic accident that killed his wife, his two-year-old daughter, and his unborn but viable child. He filed suit on behalf of the unborn child and on his own behalf for deprivation of the unborn child's companionship, society, and services. A trial court dismissed those claims and the father appealed.

Citing its own earlier decisions, the Supreme Court said that the word "person" in the wrongful death statute did not include a viable unborn child. Although the wrongful death statute did not permit an action on behalf of an unborn viable child, the father had a cause of action under a different statute for the "expense and actual loss of services, companionship and society resulting from... death of a minor child." The statutes served different functions and compensated different persons, the court said. The father's claim did not depend on the legal status of the child, the court said.

Dismissal of the wrongful death action on behalf of the unborn child was affirmed, but dismissal of the father's claim was reversed.—*Dunn v. Rose Way, Inc.*, 333 N.W.2d 830 (Iowa Sup. Ct., May 18, 1983; rehearing denied, June 9, 1983)

MD PROPERLY DISMISSED FROM RESIDENCY PROGRAM

A trial court's determination that a resident's dismissal from his program did not violate fair procedure require-

ments was proper, a California appellate court ruled.

The September and October 1979 minutes of the hospital's residency review committee meeting indicated that the resident was experiencing difficulties with patient care and interaction with committee members. The program director met with the resident and explained that the resident's promotion to chief resident depended upon improvement in these areas. Improvement occurred and the resident was made chief resident.

In March 1980, the resident informed the program directors that he would not comply with new policy requirements for consultations. Later that month, the resident received oral and written notification that he was on probation. The resident was then suspended.

In April 1980, the resident appeared before the hospital residency review committee, which was convened to determine whether the resident should be dismissed from the program. The issues at the hearing were the resident's poor communication with patients and staff, his poor attendance, his poor consultation practices, and his adverse effect on morale. Dismissal was recommended and a review committee confirmed the recommendation. In May, the resident had another hearing before a special committee, and the recommendation to dismiss the resident was affirmed. In March 1981, the resident filed an action in court for temporary relief and reinstatement. The motion was denied.

On appeal, the appellate court upheld the lower court's denial of the petition. The court stated that the hospital did not have to prove that the hospital's overall quality of medical care was lessened because of the resident. An effective educational program for all residents requires more than just good patient care. The court stated that the hospital's procedures comported with fair procedure requirements. The resident received notice of the specific changes and notice of specific instances on which the committee had based its decision. Notice of the hearing and charges was received before any action was taken. And, the resident had an opportunity to be heard before the residency review committee and before the specially convened committee.

The court noted that the hospital was not required to provide the resident with all of the procedural safeguards of an adversary trial situation. The procedures provided were adequate and the decision should be upheld, the court ruled.—*Marmion v. Mercy Hospital and Medical Center*, 193 Cal.Rptr. 225 (Cal.Ct. of App. July 19, 1983)

HOSPITAL NOT COMPELLED TO DISCLOSE PEER REVIEW RECORDS

A hospital could not be compelled to disclose records of its peer review committee to the state attorney general, a Michigan appellate court ruled.

The hospital notified the state Board of Medicine that it had completed an internal investigation of the November 7, 1981 death of a patient. The hospital's peer review committee found that a staff physician had failed to meet acceptable hospital standards. His areas of deficiency included preventable technical error in

surgery, neglect of patients, judgmental error, avoidable postoperative complications, and unprofessional behavior. As a result, the hospital suspended his staff privileges for a period of six months.

The department of licensing and regulation began conducting its own investigation of the physician. It requested the hospital to supply the information it used in conducting its internal investigation. The hospital refused on the ground that the information was privileged. A trial court issued a subpoena for the information, but the appellate court reversed.

A state law provided that records of hospital review committees were confidential and could be used only for internal peer review activities. Although the hospital was obligated to explain in general terms the reasons for its actions, the information collected by the review committee was not disclosable to the attorney general. The court said that the department's investigation was not impaired because it could interview hospital employees and staff members and obtain patient records for its investigation. The trial court's grant of a subpoena was reversed.—*Attorney General v. Bruce*, 335 N.W.2d 697 (Mich. Ct. of App., April 18, 1983)

FEMALE PHYSICIANS FAIL TO PROVE DISCRIMINATION

Female physicians employed by a university medical school failed to prove a prima facie case of sex-based discrimination with respect to salaries, a federal trial court in New York ruled.

Female physicians employed as full-time faculty members of the school brought an action on their own behalf and data of other female faculty members, charging discrimination with respect to both salaries and pensions. The physicians relied extensively upon statistics in attempting to prove their case.

Experts for the school did not agree with the conclusions of the physicians' experts and pointed out technical shortcomings in their analysis. In the face of the many shortcomings, the court found the physicians' model technically inadequate and that they failed to sustain their burden of proof as to salaries. The court dismissed the claims of pay discrimination.

The court found that the pension plan, which was based on sexsegregated mortality tables, constituted unlawful discrimination, even though the plan was optional. The court's final decision on this plan was reserved, pending further ruling by the Supreme Court on other cases involving the issues in question.—*Sobel v. Yeshiva University*, 566 F.Supp. 1166 (D.C., N.Y., June 24, 1983)

MD's PRIVILEGES SUSPENDED FOR FAILURE TO TREAT INDIGENTS

Suspension of a physician's staff privileges at a private hospital for failure to comply with a bylaw requiring that he treat indigent patients did not violate his constitu-

tional rights, a Pennsylvania appellate court ruled.

At the insistence of officials of the state health department, the hospital adopted a bylaw that required each of the three obstetrician/gynecologists to accept one-third of the indigent patients. One of the physicians refused to comply, saying he felt unable to take on an unlimited number of patients and properly care for them. His staff privileges were then suspended, pending his willingness to comply with the bylaw. A trial court refused to enjoin the suspension.

Affirming the decision, the appellate court said that the hospital's action was state action. The bylaw in question was adopted at the insistence of state officials and that was sufficient to render the hospital's action state action. While the suspension deprived the physician of his liberty interest, the bylaw was not arbitrary or unreasonable. The requirement to treat indigent patients was not a violation of substantive due process, the court concluded.

The hospital's suspension of the physician's privileges was not unconstitutional, the court said.—*Clair v. Centre Community Hospital*, 463 A.2d 1065 (Pa.Super.Ct., July 15, 1983)

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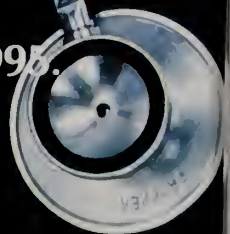
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NUESTRA PORTADA

"Contraste, Símbolos y Forma". Serigrafía del artista puertorriqueño Francisco Rivera Quiles. Esta obra gráfica se ubica dentro del contexto surrealista. Su título se refiere, de modo específico, a las opciones analíticas dentro de los elementos y principios del arte. El artista presenta, a través de estos signos, la idea de la brevedad de la vida.

Rivera Quiles nació el 17 octubre de 1953 en Cayey, Puerto Rico. Se interesa por el dibujo a los diez años de edad. Luego, se aficiona por la música e ingresa en la Banda Escolar de la Escuela Benigno Fernández García. Más adelante cursa estudios de piano con la profesora Cándida Luz Rivera.

Prosigue estudios secundarios en la escuela Miguel Meléndez Muñoz de Cayey donde se destaca al obtener en 1972, el primer premio estatal en pintura con el óleo titulado "Secando". Obtiene, además, el segundo premio regional en pintura categoría Grupo Talentosos del Festival de Bellas Artes del Departamento de Instrucción Pública y los tres primeros premios regionales en diseño de carteles auspiciado por la Administración de Veteranos y el Departamento de Instrucción Pública.

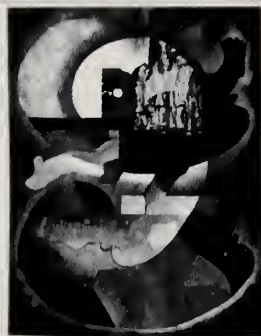
En 1973 ingresa al Colegio Universitario de Cayey en el cual se destaca como atleta, además de participar en varias exposiciones colectivas. En 1977, comienza estudios en la Escuela de Artes Plásticas del Instituto de Cultura Puertorriqueña. Contribuye con un proyecto de filosofía educativa y revisión curricular de arte, para la misma institución. Al finalizar su primer año de estudios artísticos, su obra "Ironía del Sistema" es seleccionada para la exposición anual de la Escuela de Artes Plásticas. Obtiene un bachillerato en Artes del Departamento de Humanidades del Colegio Universitario de Cayey en 1979.

Realiza estudios post-graduados en el Programa de Estudios Puertorriqueños y Centro de Investigación de la Universidad del Estado de Nueva York en Buffalo. Su proyecto en estudio tiene como título "Conceptos del Arte en Puerto Rico".

Es invitado a formar parte del Grupo Logos Infinito, organización para la Integración de las Artes y las Ciencias, con el cual participa en exposiciones colectivas.

ASOCIACIÓN MÉDICA DE PUERTO RICO

BOLETÍN



Rivera Quiles expone sus pinturas individualmente en la Convención de Ginecólogos y Obstetras en el Hotel Condado Beach en 1982. Entre otras exposiciones colectivas figuran la Quinta Bienal del Grabado Latinoamericano en 1981; Tercera y Cuarta Muestra de Pintura y Escultura Puertorriqueña 1979-1980; Biblioteca Carnegie, 1978; Museo de Casablanca, 1978; Museo de la Universidad de Puerto Rico, Recinto de Río Piedras, 1978; Colegio Universitario de Cayey, 1973 y Museo de Arte de Ponce en 1972.

Actualmente su trayectoria artística se dirige hacia la preparación de varias exposiciones en las cuales alterna la fotografía, la cinematografía y el arte experimental.

La Asociación Médica de Puerto Rico agradece a la Galería de Arte "Raíces" en la Avenida F.D. Roosevelt de Hato Rey, su interés y colaboración en la consecución de esta obra para nuestra portada.



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EDITORIAL



El Pulmón y la Industria

A través de los años se han acumulado una serie de productos químicos, tanto orgánicos e inorgánicos, en nuestras industrias que están ocasionando una serie de disturbios patológicos en el pulmón de nuestros trabajadores,⁵ muchas veces imperceptibles hasta muchos años después de la exposición original. Así vemos el caso de una trabajadora en la industria electrónica de una fábrica en nuestra isla, la cual tiene su ocupación principal en la línea de ensamblaje de monitores que se usan en las unidades de cuidado intensivo. Como parte de sus tareas diarias, esta obrera tiene que soldar diminutas conexiones electrónicas en los circuitos de estos delicados instrumentos. Para ello utiliza un cautín caliente que lo aplica a lo que parece ser una inocua pasta metálica que contiene sales de platino, sales de plata y sales de aluminio. La obrera trabaja por dos años en dicha industria sin tener problemas con su salud. Un buen día el sistema de extractores de aire de la fábrica se descompone y los obreros trabajan varios días sin estos extractores. Esa noche nuestra heroína se despierta a las dos de la mañana con un episodio espasmódico de tos seca que dura aproximadamente de treinta a cuarenta minutos y la deja exhausta. Al otro día se reporta al trabajo completamente asintomática pero por las próximas semanas y meses tiene esos episodios espasmódicos en su casa. Nuestra valiente obrera, acude en el transcurso de seis meses a varios médicos buscando un remedio a sus episodios nocturnos de dificultad respiratoria. Uno de ellos finalmente la ausculta y le encuentra sibilancias pulmonares y hace el diagnóstico tentativo de asma bronquial. Como ésta diligente trabajadora hay miles afectados en nuestra sociedad tan sumamente industrializada.

Se trata de un caso de asma bronquial extrínseca cuyo broncoespasmo responde a una inusitada hipersensitividad de los bronquios de la paciente a las sales de platino que emanan el humo producido cuando el cautín se pega a la pasta de soldadura.⁵ Hoy en día gracias a los estudios de varios investigadores podemos identificar múltiples compuestos químicos que pueden traer reacciones tanto inmediatas como tardías después de la exposición inicial a estos productos en el trabajo.^{2, 3, 4, 5, 6} Las reacciones inmediatas generalmente ocurren en un período de media hora a dos horas después de la exposición y las reacciones tardías suelen ocurrir en un intervalo de ocho a doce horas, y por lo tanto muchas de estas se manifiestan ya fuera del ambiente de la fábrica o el taller.⁵ De ahí es que muchos de estos casos pasan desapercibidos por años, ya que el médico primario no asocia estas reacciones tardías a algo que ocurrió en el ambiente de trabajo muchas veces en la mañana o en la tarde del período laboral. Sin embargo, a medida que pasa el tiempo y la obrera sigue expuesta a estos agentes nocivos puede llegar a tener los dos tipos de reacciones: en el trabajo y fuera de él. Se convierte así en una condición clínica crónica y de mayor dificultad en su manejo.

El magnífico Artículo de Repaso de Enfermedades Ocupacionales del Pulmón del Dr. Ramírez Rivera que aparece en este volumen del Boletín de la Asociación Médica de Puerto Rico, sirve para alertarnos sobre muchas de las substancias que pueden causar desórdenes respiratorios a nuestra masa laboral. Como medida de preámbulo a la lectura de este artículo sería bueno poner en perspectiva las enfermedades ocupacionales pulmonares que más frecuentemente vemos en la isla de Puerto Rico. Nos basamos en nuestra experiencia de los últimos seis años como perito consultor de la Comisión Industrial de Puerto Rico; en este período de tiempo hemos reevaluado cerca de mil ochocientos casos de enfermedades respiratorias inducidas por productos existentes en los distintos ambientes de trabajo. Aproximadamente 90% de los casos estudiados se deben a asma bronquial de tipo extrínseca. Un 5% se deben a exacerbaciones de enfermedades crónicas obstructivas pulmonares pre-existentes a la exposición en el trabajo y los casos restantes comprenden los renglones de traumas torácicos, neumonitis por hipersensitividad, enfermedad relacionada al asbesto, tuberculosis, y otras. Estos últimos renglones ocuparon aproximadamente 1% cada uno en nuestro grupo de estudio.

Ya que el asma industrial comprende el mayor volumen de nuestros casos sería bueno desglosar los subtipos de esta enfermedad que pudimos identificar. Cuatro áreas laborales son notorias en proveernos la gran mayoría de los casos de asma vistos en nuestro grupo. Estas son la industria tabacalera; los comedores escolares; el mantenimiento y limpieza en nuestras escuelas públicas y por último, la industria de la elaboración de los textiles en piezas de ropa. Diríamos que el 80% de los casos de asma estudiados por nosotros provienen de las cuatro áreas que acabamos de identificar.

El restante 10% de los casos se pudo localizar a las siguientes industrias: la industria farmacéutica, especialmente la productora de antibióticos; la industria electrónica donde activamente se utilizaron sales de plata y de platino en soldaduras; las fábricas que producen plásticos donde se usan resinas de epoxi y los isocianatos de tolueno; los almacenes elevados de distintos granos y cereales; la industria petroquímica y sus vecindades; y por último los obreros agrícolas envueltos en programas masivos de fumigación con insecticidas de tipo de fósforo orgánico.

En las grandes fábricas de tabaco localizadas mayormente en los pueblos de Caguas, Cayey y Utuado, la mayor parte de los obreros que desarrollaron alergias relacionadas a la hoja del tabaco y a su polvo eran mujeres cuyo oficio era despalillar la hoja del tabaco. Aunque la literatura es escasa en cuanto a los mecanismos que producen este tipo de alergias, hay alguna evidencia en la literatura médica que indica que los factores atópicos mediados por inmunoglobulina E pueden ser causantes de este tipo de disturbio. Los peores tipos de asma identificados con las funciones pulmonares más pobres, las vimos en este grupo de trabajadoras. En las escuelas públicas las asistentes de cocina en los comedores escolares son particularmente propensas a desarrollar asma bronquial de tipo crónico al estar expuestas a los detergentes bioactivos que poseen, muchos de ellos, enzimas derivados de bacterias como el bacilo subtilis y que contienen contaminantes de las paredes bacterianas de las cepas que dieron origen a esos enzimas.¹ De igual manera vemos a diario como más obreros dedicados a la limpieza en nuestras escuelas públicas se afectan con este tipo de condición. Se sospecha que en este grupo pueda haber sensibilización con diferentes desinfectantes y detergentes que aisladamente o en conjunto puedan estar interaccionando para causarles a estos empleados sus episodios broncoespásticos que, de no identificarse a tiempo, los van a llevar a desarrollar enfermedad crónica obstructiva pulmonar.

En la industria de los textiles ya la situación se vuelve más compleja para identificar los factores etiológicos que producen el asma en estos obreros. En los ambientes de trabajo hay infinidad de fibras naturales y sintéticas que pueden dar origen a reacciones de hipersensitividad bronquial que pueden conducir al asma bronquial. Me refiero a fibras tales como el algodón, Kapok (fibras naturales derivadas de un árbol proveniente de Indonesia que sirve para rellenar paredes de bolsas, frisas, y sacos de dormir), polyester, dacron, rayon, y otras fibras sintéticas. La fibra que más se ha estudiado es la fibra del algodón y se ha establecido que esta fibra al ser inhalada produce en los mastocitos y basófilos pulmonares una liberación de histamina. Es la histamina, la que luego lleva a la reacción aguda broncoespástica. Tradicionalmente se ha dicho que estos obreros empeoran el primer día de la semana cuando regresan a sus fábricas. Esto se explica debido a que muchas de estas fábricas permanecen cerradas durante el período de fin de semana y la concentración de fibras en el aire en la fábrica cerrada es muy alta. Estos pacientes mejoran a medida que la semana va evolucionando hacia el viernes. Ya hay alguna evidencia, que síntomas respiratorios pueden permanecer aún cuando el paciente se retire del trabajo.⁹

Es pertinente un comentario acerca de los insecticidas. Anualmente se refieren muchos obreros envueltos en el riego de insecticidas en programas de fumigación masiva en diferentes áreas agrícolas, muchos de estos obreros al ser expuestos a estos productos desarrollan episodios broncoespásticos que pueden ser agudos o pueden ser retrasados y

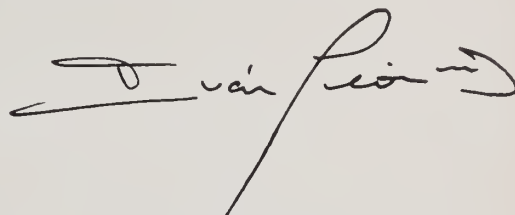
ocurrir en sus hogares varias horas luego. Ultimamente se ha podido incriminar a los insecticidas que contienen fósforo orgánico como el agente causal de este tipo de reacciones. Estos químicos son substancias que actúan como anticolinesterasas y que juegan un papel importante al permitir que substancias colinérgicas que normalmente serían eliminadas por la colinesterasa, permanezcan activas y actúan como agentes broncoespásticos.¹ En la evaluación de estos casos, como de cualquier otro caso donde se sospecha que una exposición industrial pueda causar la enfermedad respiratoria, las pruebas de reto bronquial ("Bronchial Challenge") son de particular importancia.^{1, 2} Mediante esta prueba se obtiene una espirometría basal y luego se expone al paciente al agente sospechoso en una cámara aislada del cuarto del laboratorio; subsiguientemente se mide a intervalos de cinco minutos la espirometría para determinar si hay una caída en el volumen forzado espiratorio en un segundo. Una prueba positiva sería aquella en que el volumen forzado espiratorio en un segundo cae a 20% o menos del valor basal. Obviamente estas pruebas hay que hacerlas en un ambiente hospitalario donde se pueda seguir al paciente con pruebas bronquiales después de las primeras tres o cuatro horas a través de todo el día y toda la noche para así poder detectar reacciones tanto tempranas como tardías. En manos expertas estas pruebas son seguras y le proveen al clínico un método diagnóstico relativamente rápido para establecer el diagnóstico de enfermedades pulmonares. Mediante estas pruebas se pueden probar productos farmacéuticos en aerosol y se puede estudiar su efecto sobre las reacciones broncoespásticas en el obrero particular. Por ejemplo, muchas de las reacciones broncoespásticas inducidas por las sales complejas de platino se pueden suprimir premedicando al obrero con la cromolina sódica.³ Esta substancia no solo evita las reacciones tempranas sino que también tiene un poder de suprimir las reacciones tardías en estos obreros y por lo tanto representa en el armamentario farmacológico una droga segura y efectiva para el tratamiento de muchas de estas reacciones. De esta manera al obrero salir del laboratorio de función pulmonar ya el clínico está en la completa certeza de que el agente terapéutico va definitivamente a mejorar a su paciente.

Las neumoconiosis o enfermedades pulmonares relacionadas a la inhalación de partículas inorgánicas tales como silicas, polvo de carbón, y polvo de berilio, son extremadamente raras en nuestra isla dado el caso de que no tenemos una industria minera establecida. Sin embargo, varios años atrás surgió un brote de casos de silicosis en obreros que trabajaban en una industria que elaboraba tazas de porcelanas que luego se utilizaban en la industria hotelera. Varios obreros desarrollaron la fibrosis típica de esta enfermedad y en muchos casos se detuvo el progreso de la enfermedad al cesar la exposición y al cerrar la fábrica. Otros obreros fueron menos afortunados y todavía presentan las secuelas incapacitantes de una enfermedad crónica restrictiva pulmonar debido a esa exposición que pasó desapercibida. La silicosis también puede ocurrir en nuestro medio ambiente en los técnicos o asistentes dentales que usan polvo finos para esmerilar y pulir superficies dentales esmaltadas.⁴

En nuestro grupo de mil ochocientos casos de enfermedades respiratorias hemos vistos cuatro casos de enfermedades relacionadas al asbestos. Tuvimos un caso de un mesotelioma en un obrero que trabajaba en las calderas de una planta de energía eléctrica. La radiografía de tórax del obrero claramente revelaba placas pleurales además del mesotelioma. En los remanentes tres casos uno de ellos presentaba un ligero aumento en las marcas broncovasculares basales pero su función pulmonar era enteramente normal. Los otros dos casos representaron engrosamiento pleurales definidas. Reconocemos definitivamente que nuestra muestra es una completamente prejuiciada ya que solo se nos refieren los casos que son evaluados por el Fondo del Seguro del Estado y que se envuelven en el proceso de litigio. Por lo tanto por cada caso que vemos y, basados en experiencias en otros países que tienen industrias similares a las nuestras, calculamos que hay dos casos más por cada caso que vemos anualmente en nuestro grupo de trabajo. Actualmente estamos siguiendo a veintinueve obreros de una industria petroquímica en Cataño que han estado expuestos a fibras de crisólito (una de las formas de asbestos) por espacio de veinte años. Es curioso notar que las radiografías seriadas junto a exámenes físicos y a espirometrías por los últimos diez años no han revelado indicio alguno de enfermedad relacionada al asbestos. Quizás en esos casos todavía no ha pasado el tiempo de latencia necesario para desarrollar la enfermedad en estos obreros.⁷ También cabe la posibilidad de que factores genéticos jueguen un papel significativo en el desarrollo de enfermedad fibrótica del pulmón. Es probable exista un gene que promueva el desarrollo de esta susceptibilidad para depositar fibras de colágeno de forma anormal al exponerse los pulmones susceptibles a la fibra de este material.⁸ Todo esto es especulativo pero sirve como estímulo a investigadores locales e internacionales en la búsqueda de los mecanismos intrínsecos que producen estas enfermedades ocupacionales.

Esperamos que la identificación de las áreas problemáticas en nuestros talleres de trabajo sirvan a las agencias gubernamentales responsables por fijar normas de seguridad de trabajo y de seguimiento de pacientes para elaborar guías más estrictas y mecanismos de comprobación de que estas medidas se están llevando a cabo en el

ambiente industrial para protección de nuestros obreros. No solo estas agencias tienen la responsabilidad de velar por la salud de nuestros compañeros obreros sino que los médicos primarios, especialistas y personal de enfermería tienen a su vez el mandato moral y profesional de adquirir historiales de exposición a diferentes químicos en nuestras industrias para así poder llegar a un diagnóstico más temprano y a un mejor tratamiento y prevención de estas enfermedades que tanto daño pueden hacer a una masa obrera joven y vigorosa.



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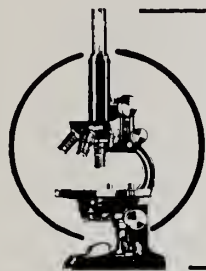
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PATHOLOGY *Review*

Maria Castillo Staab, M.D.*

Un hombre de 40 años fue intervenido quirúrgicamente y se le encontró un pólipo adenomatoso en el colon izquierdo.

Esta lesión se ilustra en la figura 1.



Figura 1: Pólipo adenomatoso pedunculado del sigmoide.

Los pólipos adenomatosos:

- a) son lesiones precancerosas
- b) requieren seguimiento con enemas de bario para detectar nuevos pólipos
- c) requieren resección de la porción del intestino donde se encuentra el pólipo
- d) requieren colonoscopia más profunda en busca de pólipos adicionales
- e) se pueden ignorar ya que no están relacionados con el desarrollo de cáncer del colon

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Polipo Adenomatoso del Intestino Grueso

El origen de los pólipos intestinales puede ser tumoral, inflamatorio y metaplásico o hiperplásico. Las lesiones tumorales representan proliferación del epitelio glandular del intestino, por lo cual se denominan adenomas. Hay dos variantes histológicas principales: el llamado pólipo adenomatoso y el adenoma vellosos.

El pólipo adenomatoso es el tumor más común del intestino grueso. Representa el 75% de todos los adenomas. La mayoría ocurren en el recto, siguiendo en orden de frecuencia el sigmoide, colon izquierdo, colon transversal, colon derecho y ciego.

Estas lesiones siguen la misma distribución anatómica que el carcinoma de colon y suelen aparecer en el mismo grupo etáreo. Aunque estudios en especímenes de autopsia demuestran que solamente 5% de los pólipos adenomatosos presentan cambios de malignidad, se asume que el cáncer de colon se origina en un pólipo adenomatoso.

Es importante hacer notar que el riesgo aumenta con el tamaño de la lesión (pólipos que miden más de 1 cm.), con el número de pólipos presentes o extirpados y con la presencia de un patrón histológico de adenoma vellosos.

Los pólipos adenomatosos pueden ser sésiles o pedunculados (Fig. 1) y varían en tamaño desde 2 milímetros hasta 3 centímetros. Inicialmente estas lesiones son sésiles y se hacen pedunculadas debido a la peristalsis intestinal pero muchas permanecen sésiles. Microscópicamente los pólipos adenomatosos consisten de estructuras tubulares formadas por el epitelio del intestino grueso.

Los núcleos aparecen apiñados e hiper cromáticos y las células presentan siempre cierto grado de atipia y un número variable de mitosis. Las células exhiben además disminución en la producción de moco intestinal.

En ocasiones el atipismo celular y el desarreglo estructural de las glándulas son suficientemente severos y establecen el diagnóstico de carcinoma intramucoso. Debemos recordar que cambios malignos limitados a la mucosa de un pólipo (carcinoma in-situ o intramucoso) representan un diagnóstico histológico y no un diagnóstico biológico de cáncer ya que la mucosa del colon no posee vasos linfáticos. Es por esto muy importante que el

patólogo oriente las secciones del pólipo para incluir la *muscularis mucosa* y el tallo o pedúnculo de los pólipos. La presencia de glándulas malignas debajo de la *muscularis mucosa* presume la posibilidad de metástasis a través de canales linfáticos. Los factores de valor pronóstico más importantes en el carcinoma en pólipos adenomatosos son la longitud del pedículo y el tamaño del pólipo.

Los pólipos de menos de 1 centímetro tienen una incidencia de malignidad invasiva de 1%. Los que miden de 1 a 2 centímetros, una incidencia de 10.2% y los pólipos adenomatosos de más de 2 centímetros presentan evidencia de malignidad invasiva en un 35%.

Los pólipos intestinales de tipo vellosos (Fig. 2) ocurren con menor frecuencia que los adenomatosos. La mayoría se encuentra en el recto y son lesiones solitarias. Alcanzan un tamaño mayor y pueden medir hasta 10 centímetros. Casi siempre son sésiles. Microscópicamente están compuestos de células columnares arregladas formando papilas altas y delicadas productoras de moco intestinal. La secreción de moco puede ser en ocasiones tan abundante que provoque síntomas por pérdida de potasio.

Los adenomas vellosos sufren transformación maligna 10 veces más frecuente que los adenomatosos. La poliposis intestinal familiar es una enfermedad hereditaria en la cual los pacientes presentan cientos de pólipos de diferentes tamaños en el intestino grueso. Todos estos pacientes desarrollan carcinoma del colon.

Los pólipos adenomatosos pueden extirparse quirúrgicamente haciendo una polipectomía por endoscopia cortando la base del pólipo o practicando una resección del segmento de colon donde se encuentra el pólipo seguido de anastomosis. Este procedimiento es el recomendable para el tratamiento de los pólipos sésiles.

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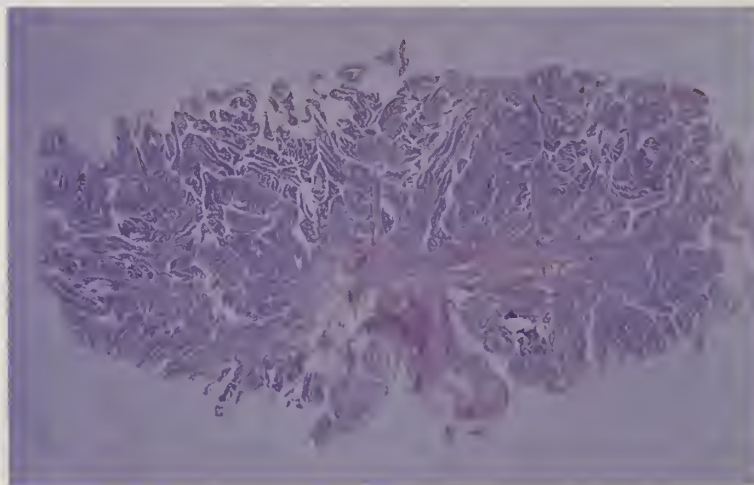
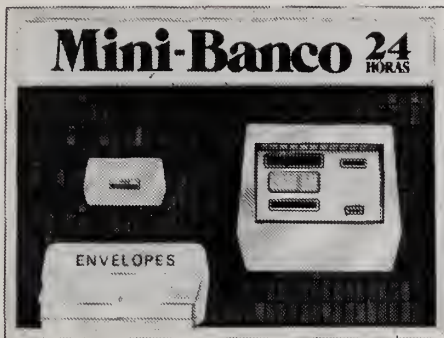


Figura 2: Detalle microscópico de un adenoma vellosos.

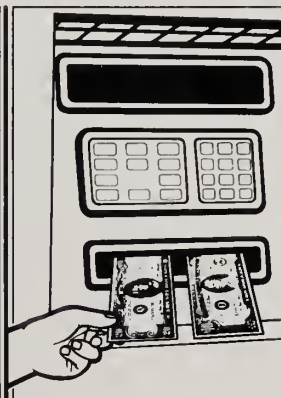
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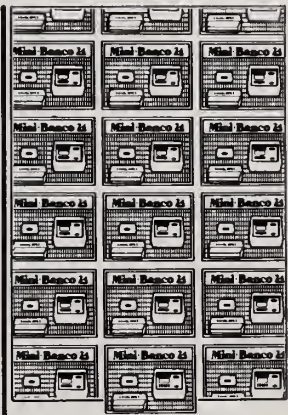
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What can you do for hypertensives like Mary B?

Uncontrolled

Moderate hypertension (160/110 mmHg) with recent increases despite medication.

Forgetful

Misses appointments and frequently fails to follow instructions.

Overweight

At 73 largely sedentary... weight even more of a problem now.

Coexistent diabetes

On daily insulin after diet, exercise, and oral agents failed.



Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Mary B represents 2,165 women over 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Mary B's difficult age group.²

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Use in diabetes

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta-blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.³⁻⁶

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁷ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Mary B...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

* Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.



ONE TABLET A DAY TENORMIN® (atenolol)

For Mary B...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyroidosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended

human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometric tests.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on file, Stuart Pharmaceuticals. 2. Herman RL, Lamdin E, Fischetti JL, Ko HK. Postmarketing evaluation of atenolol (Tenormin®). A new cardioselective beta-blocker. *Curr Ther Res* 1983; 33(1):165-171. 3. Deacon SP, Barnett D. Comparison of atenolol and propranolol during insulin-induced hypoglycemia. *Br Med J* 1976; 2:272-273. 4. Lighman SL, et al. Effects of beta-blockade and naloxone on the hormonal and cyclic AMP responses to hypoglycemia in man. *Br Med J* 1983; 65(3):21P. 5. Lauridsen UB, Christensen NJ, Lyngsø J. Effects of nonselective and beta₁-selective blockade on glucose metabolism and hormone responses during insulin-induced hypoglycemia in normal man. *J Clin Endocrinol Metab* 1983; 56:876-882. 6. Ryan JR, et al. Response of diabetics treated with atenolol or propranolol to insulin-induced hypoglycemia. *Drugs* 1983; 25(suppl 2):256-257. 7. Zacharias FJ. Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980; 6(suppl 1):86-89.



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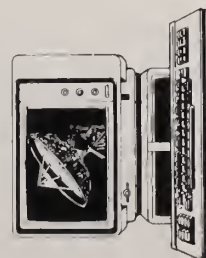
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ESTUDIOS CLINICOS

Rectal Prolapse: A Retrospective Review At University District Hospital

Luis A. Morales-Otero, M.D.
Pedro J. Roselló, M.D., FACS, FAAP

Abstract: Twenty-one cases of true rectal prolapse diagnosed and treated at the University District Hospital during the period of 1971-1983 were retrospectively reviewed. The factors evaluated in these cases include age, clinical presentation, associated conditions, treatment modalities, complications and results. Rectal bleeding was the most common sign encountered, while discomfort and/or pain were the symptoms patients most commonly complained of. True prolapse was documented in all 21 patients according to the Altemeier classification. Psychiatric condition is a commonly associated factor among the adult group. Surgical treatment in these patients was widely varied. We found that this condition is rare in our patient population and that there is no one preferential or specific surgical treatment utilized.

In view of the diversity of presentation and treatments available, each patient should be treated according to his individual clinical condition.

Rectal prolapse is a relatively uncommon occurrence in which some or all of the layers of the rectum extrude through the anus. When evaluating patients with this possible diagnosis we must differentiate between true procidentia (protrusion of the rectum in circular rings through the anal sphincter) and false procidentia, which is protrusion only of rectal mucosa in folds through the anus. Throughout the years a wide variety of surgical procedures have been used as modes of therapy for this condition.

In order to evaluate the clinical presentation and the surgical treatment used at our Institution, we set out to study retrospectively all cases of rectal prolapse between the period of 1971-83. These data form the basis for our study.

MATERIALS AND METHODS

All records with the diagnosis of rectal prolapse filed in the Record Room of the University District Hospital for the period of January 1971 through August 1983 were evaluated in this study. A total of 33 records were

identified, 10 of them were noted to have mucosal prolapse only and therefore were excluded. Also discarded were two cases of true prolapse not treated surgically. The remaining 21 cases of surgically managed true prolapse were reviewed for such data including age, signs and symptoms, physical findings, associated conditions, treatment, complications, length of hospitalization, mortality, results, and follow-up.

RESULTS

1. **Sex distribution:** there were 15 females (71%) and 6 males (29%). The ages ranged from 4 months old to 87 years old, mean age 51.8.

2. **Signs and symptoms:** of the 21 patients studied, 7 suffered from rectal bleeding (33%), 3 from constipation (14%), 3 from incontinence (14%). Among the symptoms, rectal discomfort and pain were found in 10 patients (47.6%) and a feeling of loss of pelvic support in 7 patients (33%).

3. **Physical findings:** thirty-three patients were originally found diagnosed with rectal prolapse. Among these, 21 patients had true prolapse according to Altemeier's classification.¹ Of the remaining, 3 adults were found to have rectal prolapse less than 3cm, representing false prolapse (Altemeier Type I), and 7 children were noted to have mucosal prolapse following reconstructive surgery for imperforated anus. These were excluded from the review. Also excluded were 2 adults with true prolapse who were discharged home because of an aggressive psychiatric condition who were not surgically intervened, and had no documented follow-up.

Decreased sphincter tone was a common physical sign documented in 10 patients (47.6%).

4. **Associated conditions:** the most commonly associated condition among the adult group was a major psychiatric illness, occurring in 6 patients (29%). The second most common associated condition was previous surgical and gynecological procedures. Four patients had procidentia uteri and/or cystocelle, and 4 others had a previous history of uterine, ovarian, or colorectal surgery (Table I) (19% each). In the group of 3 children, 1 was mentally retarded, 1 had bladder extrophy, and one had a common cloaca with double vagina.

From the Surgical Research Laboratory and the Department of Surgery, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

TABLE I

Associated Conditions in Adults

Psychiatric Conditions	6
Cystocelles or Procidencia Uteri	4
Hysterectomy, Ovarian or Colo Rectal Surgery	4
Chronic Pulmonary Condition	
(Bronchial Asthma)	1
Total Adult Patients	18

5. **Treatment:** there was a wide range of surgical procedures performed on these 21 patients. In the pediatric group, one was treated by repeated manual reduction and subsequently recurred. One had a prerectal packing procedure, and another had a perineal anoplasty. There were no recurrences in the surgically treated cases.

The adult group consisted of 18 patients. One was deemed inoperable due to a high operative risk. There were 19 surgical procedures done in the remaining 17 patients (Table II). In the initial procedures, 5 Ripstein sling operations were done with one recurrence, six anterior resections (with or without fixation) with 2 recurrences, two suture fixations of the sigmoid to the sacrum were there done with no recurrences, one transrectal resection performed which did not recur, and initially 3 perineal ring repairs were done with no recurrence reported. In the above group of initial procedures, two patients who underwent anterior resections had to be re-operated completing the 19 surgical procedures of the study. Both patients underwent perineal ring repairs, and one of them recurred at follow-up.

6. **Operative complications:** there were 4 major complications for a 19% incidence in the operated group; an episode of septic shock, a iatrogenic bladder rupture, a prolonged postoperative ileus, and a persistent perineal foreign body reaction. There was no operative or postoperative mortality related to these procedures.

7. **Follow-up:** the follow-up ranged from 3 months to 10 years. We found six recurrent or persistent prolapses. The 2 persistences occurred in the 2 patients (1 adult, 1 child) treated nonsurgically. There were recurrences in two of six patients who underwent low anterior resections (33%); one of five patients with Ripstein's procedures (20%). The overall incidence of recurrence after surgical interventions in the adults was 21%.

TABLE II

Adult Patients: Treatment

Initial Procedures	Number	Recurrence
Ripstein Sling	5	1
Anterior Resection ± Fixation	6	2*
Suture Fixation Sigmoid to Sacrum	2	0
Transsacral Resection	1	0
Perineal Ring Repair	3	0
Reoperation After Recurrence		
Perineal Ring Repair	2*	1

*Patients that recurred after the initial procedure

DISCUSSION

The therapeutic approach to rectal prolapse has been a long standing controversial subject. Related to this has been the multitude of surgical procedures which have been advocated, none of which has demonstrated a marked superiority in all case of true rectal prolapse.

In explaining the pathogenesis of the entity two theories have dominated in the controversy. Moschowitz in 1912 described a mechanism of a sliding hernia to explain rectal prolapse.² More recently, a rectal intussusception theory supported by Theuerkauf and others from Mayo Clinic has gained strength.³ Using these as the basis to explain the anatomic defects involved, a number of procedures have been utilized for rectal prolapse in an attempt to correct these underlying abnormalities.

In general, the management of this entity can be classified as medical or surgical. The surgical procedures can be classified according to the approach utilized; either abdominal, perineal, combined abdomino-perineal or transsacral.

The abdominal procedures used include resection of the redundant sigmoid colon, fixation of the colon and rectum, and direct repair of the pelvic musculature.

Theuerkauf has supported the sigmoid resection³ based on a series of 124 patients treated surgically during a 16 year period at the Mayo Clinic. In this series, 28 patients underwent anterior resection with one death and one recurrence (3.7%); 68 underwent suspension and fixation of the sigmoid colon with recurrence in 22 (32.4%); and 13 underwent the Altemeier procedure, resection of the recto-sigmoid through a perineal approach with recurrence in 5 (38.5%).

Other technical variations commonly utilized among the abdominal approaches have been fixation of synthetic materials such as an Ivalon sponge, or by the Ripstein procedures.⁴ In the hands of Wells, the propulsor of the Ivalon polyvinyl sponge procedure, this technique has been highly successful with a 1.9% recurrence and a 3.7% mortality in a series of 266 patients at St. Marks Hospital in London.³

Nigro and associates utilize a puborectalis sling suspension through the abdominal approach.⁵ A teflon sling is sutured to the posterior and lateral walls of the rectum and fixed anteriorly to the pubic tubercles. His results in 60 good risk patients were excellent, with no recurrence. This procedure is contraindicated in young females who may become pregnant.

Altemeier's own experience with a perineal sigmoid resection produced results different from those of the Mayo Clinic.¹ In his 19 years experience with 106 patients only 3 developed recurrence with no mortality. Others have been unable to reproduce such results. Friedman's experience with 27 patients undergoing 33 Altemeier procedures showed an overall recurrence rate of 50% during a 1 to 17 years follow-up period.⁶ They concluded that their results were unsatisfactory, although the procedure was well tolerated by the elderly and could be reserved for these high risk patients.

Thomas⁷ described his transsacral approach by excision of the coccyx and the 5th vertebrae. This is a rectopexy with repair of the levator ani anteriorly, with

fixation of the rectum laterally to the levators and posteriorly to the dense sacral fascia, and repairing superiorly of the peritoneum of the cul de sac. There was a 20% wound infection rate, no recurrences and no mortality in this group of 44 patients.

The Thiersch operation⁴ described in 1891, involves the encirclement of the anal orifice with wire suture. This simple operation has been reserved for elderly and high risk patients. An undesirable effect of this procedure is that if the wire is placed too tightly, there is a tendency to difficult fecal passage with resulting fecal accumulation. Subsequently, the procedure was then modified by replacing the wire with several types of synthetic materials such as teflon or polyethylene.

In reviewing the literature it becomes clear that the surgical procedures for rectal prolapse have been varied and that no consensus of opinion exists as to the most appropriate one. Each author describes his own procedure with good results. However, frequently these same procedures in other hands appear difficult and with unsatisfactory results.

In our retrospective review we have found rectal prolapse to be a rare condition, occurring only in 23 cases over a 24 year period at a large referral hospital, more prevalent in the extreme ages of life, and more common in women. The most commonly associated condition among the adult group was a psychiatric condition. This appears to be a common finding in other series, as for example, in the Thomas experience, where 38 of the 44 patients, were mental cases.⁶ Within the group of women in these series, previous surgical procedures were also common associated conditions.

The treatment among adults in our series has been comparable in number and variety with those reported in the literature. At least five different techniques were used. The recurrence rate in our total number of operations was 21%.

In conclusion, based on our own results and those reported in the literature, we do not consider that at the present moment there is a specific or ideal surgical treatment for all cases of rectal prolapse. It is necessary to carefully evaluate each patient for factors including age, sex, associated conditions, and overall surgical risk in order to select the procedure of choice on an individual basis. The surgeon should therefore include several of these alternative procedures in his armamentarium.

Resumen: Se revisaron retrospectivamente 21 casos de prolapso rectal que fueron diagnosticados en el Hospital de Distrito Universitario durante el período comprendido entre enero 1971-1983. Los factores evaluados en estos casos incluyen edad, cuadro clínico, condiciones asociadas, modalidad de tratamiento, complicaciones y resultados. Se encuentra que el sangrado rectal es el signo más común, mientras que dolor y molestia rectal son los síntomas más comunes. Utilizando la clasificación de Altemeier, el prolapso verdadero de recto fue documentado en los 21 pacientes. Entre los adultos, trastornos psiquiátricos fueron hallazgos comunes. En cuanto a métodos de tratamiento, hubo una gran variedad de abordajes quirúrgicos. Encontramos que esta condición es rara en nuestra población de pacientes y que no hay un

procedimiento preferencial de tratamiento. En vista de la diversidad de presentaciones y de tratamientos aceptables, cada paciente se debe tratar concorde a su condición clínica individual.

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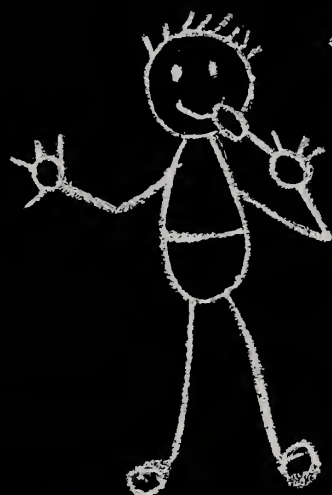
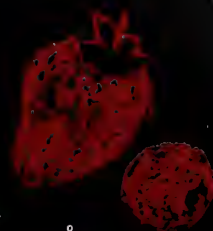
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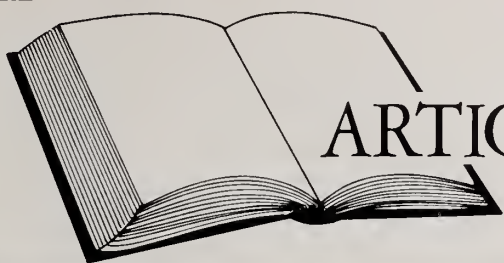
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ARTICULOS DE REPASO

Las Enfermedades Ocupacionales del Pulmón

José Ramírez Rivera, M.D., FACP*

Resumen: El artículo resume los conceptos fundamentales envueltos en el desarrollo de las enfermedades ocupacionales del pulmón y describe algunas de las enfermedades más comunes causadas por la inhalación de partículas inorgánicas (silicosis, asbestosis), por partículas orgánicas (asma, bisinosis, bagazosis) y por gases tóxicos (bronquiolitis, edema pulmonar). La destrucción irreversible del tejido pulmonar en la silicosis y la asbestosis y la necesidad de medidas para prevenir estas enfermedades es enfatizada. Un historial ocupacional cuidadoso así como radiografías y espirometrías seriadas ayudan a establecer el diagnóstico acertado. Se discuten los conceptos esenciales del tratamiento de las enfermedades ocupacionales del pulmón.

Mucho se ha aprendido sobre las enfermedades ocupacionales desde que Georgius Agricola describió en el 1556 la relación entre la minería de oro y plata en las montañas de Bohemia y síntomas pulmonares. En la treintena de los 1890 al 1920 se establecieron en Inglaterra y los Estados Unidos leyes para compensar a trabajadores víctimas de su ocupación. En décadas recientes el diagnóstico de enfermedades ocupacionales se ha multiplicado en los países industrializados. Se ha establecido el principio de concentraciones máximas aceptables. Se aprecia cada vez más ampliamente la importancia de experiencias repetidas y prolongadas como requisito para lastimar el tejido pulmonar de una manera clínicamente aparente y fisiológicamente importante (Tabla I).

TABLA I

Enfermedades que se desarrollan después de experiencias repetidas

Presentación Clínica	Substancias Tóxicas	Ocupaciones en (lista parcial)
Disnea persistente Fibrosis pulmonar	Silice, asbesto, berilio, partículas orgánicas	Minería, picadores de piedra aleaciones de metal.
Bronquitis crónica Enfisema	Cigarrillos, polvillo de algodón y de carbón, solventes, cadmio	Industria textil, producción o reparación de baterías, soldadura, uso de solventes
Cáncer del pulmón	Asbesto, arsenico, níquel, uranio	Trabajo de aislación, fundiciones refinamiento de níquel, minería de uranio
Cáncer de la vejiga	Naftilamina, benzidina	Industria química y textil. Manufactura de cueros y materiales de goma.
Neuropatía periférica	Plomo, arsénico	Producción y reparación de baterías fundiciones, pintura, manufactura de zapatos, insecticidas.
Cambios de comportamiento	Plomo, mercurio, manganeso, solventes	Reparación de baterías, producción de rayón, reparación de instrumentos científicos, manufactura amalgama dental
Síndromes extra piramidales	Disulfito de carbón, manganeso	Producción de rayón, reparación de baterías, fundiciones
Leucemia Anemia aplástica	Bencina, radiación	Laboratorios, ebanistería, ambientes con radiación

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Las enfermedades ocupacionales ocurren al inhalar partículas nocivas o gases tóxicos que resultan del proceso industrial. En Puerto Rico la inhalación de materiales alergénicos generados durante la manufactura y envase de antibióticos y vitaminas presentan un riesgo especial. Estos riesgos no son solamente del obrero. Sus familias pueden ser adversamente afectadas por partículas nocivas que entran al hogar en la ropa de trabajo. Un niño de cinco años puede tener una enfermedad ocupacional, aunque el vector, su padre, no la tenga.

Este ensayo revisa someramente los principios envueltos en el desarrollo de enfermedades ocupacionales del pulmón y discute más ampliamente algunas de las enfermedades más importantes.

Conceptos Fundamentales

La reacción a sustancias inhaladas puede ocurrir a dos niveles: las vías respiratorias y el parénquima pulmonar. Con alguna frecuencia se observan reacciones en ambos niveles, ocasionalmente se asocia una reacción pleural.

El tamaño de las partículas y su concentración, o la concentración de gases, su solubilidad y el tiempo de exposición, son importantes individualmente y en conjunto. El efecto de estos factores guarda relación con la susceptibilidad individual y la inhalación habitual de otras sustancias irritantes o tóxicas, tales como el humo del tabaco.

Las partículas mayores de 10 micras de diámetro ordinariamente impactan en la nariz, la garganta, las vías respiratorias altas y son removidas por la escalera mecánica mucociliar. Partículas pequeñas, especialmente aquellas con un diámetro entre 0.5 y 2.5 micras, flotan con más facilidad en la corriente de aire y frecuentemente alcanzan a depositarse en la periferia pulmonar al nivel bronquial o alveolar.

Los gases irritantes actúan tanto en las vías respiratorias altas como en las profundidades del pulmón, los altamente hidrosolubles, tales como amoníaco y cloro, generalmente lastiman o corroen la mucosa de las vías respiratorias altas produciendo irritación nosofaríngea y tos, con o sin flema, que puede durar de días a semanas. Los gases menos solubles, tales como fosgeno y el dióxido o el tetróxido de nitrógeno, generalmente alcanzan los bronquiolos respiratorios y los alveolos lastimando el tejido que participa en el intercambio de gases.

Gases tóxicos no irritantes, como son el monóxido de carbono, el óxido de plomo y los hidrocarburos se incorporan directamente a la hemoglobina de las células rojas, se depositan en la médula ósea y en nervios periféricos o se disuelven en la grasa del sistema nervioso central, causando daño a sistemas vitales sin identificar claramente su presencia en la puerta de entrada, el pulmón.

Analizamos a continuación algunas de las enfermedades causadas por los tres tipos de sustancias nocivas inhaladas: *las partículas inorgánicas, las partículas orgánicas y los gases tóxicos.*

Enfermedades Causadas por Partículas Inorgánicas

Los historiales de trabajadores que desarrollan estas enfermedades se remontan, por lo general, a 20 o más

años. Las reacciones tisulares una vez establecidas no son reversibles. La enfermedad se puede detectar antes de que surjan síntomas a través de radiografías seriadas y de mediciones de función pulmonar. Es importante educar a la industria y al trabajador sobre la irreversibilidad del daño causado por las partículas inorgánicas para que se practique el uso de mascarillas y se elimine el polvo nocivo del microambiente hasta donde sea posible.

La reacción del pulmón la determinan cinco factores: la naturaleza del polvo, su tamaño, su concentración en el microambiente, la duración de la exposición y la susceptibilidad individual. Hay polvos inorgánicos relativamente inertes, tales como el hierro y el bario. Al otro extremo están los polvos de sílice y asbestos, que pueden causar síntomas clínicos, y severas limitaciones funcionales, aún cuando la radiografía esté casi normal.

Silicosis

La silicosis es la enfermedad ocupacional más antigua conocida. Es una enfermedad común, pues materiales con sílice se usan en construcción, en la manufactura de cerámica y como abrasivos. Más de un millón de personas en los Estados Unidos trabajan en ambientes con suficiente sílice para producir silicosis. En Puerto Rico la enfermedad es endémica entre los que se dedican a trabajar lápidas de mármol o a hacer losetas. Puede ocurrir entre los que limpian edificios usando arena a presión.

La radiografía del tórax se caracteriza por múltiples nódulos bien delineados y de densidad uniforme que miden de 1 a 10 mm. de diámetro. La enfermedad progresa de esta presentación "sencilla" a "silicosis complicada" al conglomerarse y fundirse múltiples nódulos en masas de bordes irregulares que pueden exceder por mucho 1 cm. de diámetro (Fig. 1). Estos



Figura 1. Silicosis: Conglomeración de múltiples nódulos en masas de bordes irregulares.

nódulos usualmente se desarrollan en los lóbulos superiores. Al contraerse los mismos en la dirección del hilio aparecen múltiples hiperlucencias en la periferia del pulmón. Los ganglios parahiliares pueden agrandarse. La arteria pulmonar se dilata como resultado de la hipertensión pulmonar que finalmente causa fallo del ventrículo derecho.

La silicosis nodular simple es generalmente asintomática. Llevan el paciente al médico síntomas causados por el cigarrillo o el malestar general asociados con la reacción autoinmune. En silicosis avanzada ocurren tos, expectoración y disnea de esfuerzo. Puede haber dolor torácico, pérdida de peso y hemoptisis. Se forman cavernas cuando el proceso fibroso compromete el riego sanguíneo y se desarrolla una necrosis isquémica. Una vez se instaura el cuadro clínico avanzado, el deterioro de la función respiratoria puede ocurrir rápidamente.

Observaciones recientes sugieren que mecanismos inmunológicos son responsables por la reacción tisular.¹ La partícula de sílice se cubre de proteínas y actúa como un antígeno no específico. Usualmente se requiere de 10 a 20 años de exposición a micropartículas de sílice para que aparezcan manifestaciones radiográficas importantes. Cuando la reactividad inmunológica está aumentada, dramáticas reacciones pulmonares pueden verse en menos de tres años. Los obreros con enfermedad reumatoide expuestos a sílice desarrollan una nodularidad particular, más dispersa y más marcada.² Estos nódulos discretos de histología reumatoide pueden confundirse radiográficamente con cáncer metastásico (Figura 2).



Figura 2. Síndrome de Caplan: Discretos y dispersos nódulos reumatoides que pueden sugerir carcinoma.

Los médicos adversos a la compleja tecnología contemporánea deben regocijarse de que esta brillante relación clínica, entre la exposición a sílice y la exagerada reacción reumatoide en el pulmón, el Síndrome de Caplan, fue establecida 30 años atrás por un radiólogo en la práctica privada en la región carbonífera de Gales, Gran Bretaña, usando como único instrumento sus ojos.

Asbestosis

El término asbesto se refiere a unas fibras con un alto contenido de silicatos de hierro, magnesio y aluminio cuya resistencia al fuego y al deterioro se han conocido desde la antigüedad.

Durante los últimos 20 años se ha desarrollado la apreciación que aún concentraciones bajas de asbestos pueden ser nocivas. Recientemente, hubo una discusión amplia en al prensa sobre el cierre y la destrucción de salones de clase que se habían construido de bloques de cemento conteniendo asbesto. Increíbles concentraciones de asbesto, de hasta 170 nanogramos por metro cúbico de aire, han sido recientemente valorizados en un edificio de diez años poco ventilado, con un estucado de asbesto en el cielo raso y losetas de asbesto-vinil.³

La fibra de asbesto es larga y su inhalación depende de su peso ligero y su pequeño diámetro. El asbesto produce cambios tisulares que hacen sospechar su presencia en la radiografía sencilla del tórax. La fibrosis ocurre particularmente en las bases y una pleuritis obliteratora usualmente acompaña la reacción parenquimatosa. En la mitad de los casos en etapas avanzadas se ven placas pleurales, particularmente en los diafragmas. Alrededor de un veinte por ciento de estas placas se calcifican.

La limitación respiratoria causada por asbestosis es severa e irreversible. La disnea de esfuerzo, los estertores en las bases y el desarrollo de dedos en palillos de tambor pueden preceder por años los cambios radiográficos que sugieren el diagnóstico. El trastorno pulmonar fisiológico predominante es restrictivo, pero a menudo también es obstructivo. El obrero con asbestosis tiene un mal pronóstico pues no hay tratamiento específico para la enfermedad. El riesgo de desarrollar cáncer del pulmón en los que fuman es 90 veces más que el de la población no fumadora. El cáncer del pulmón es ordinariamente de células de avena o anaplásico, pero la prevalencia de tumores escamosos y adenocarcinoma están también aumentadas.⁴ De interés es la relación causal que existe entre la exposición al asbesto y los mesoteliomas de la pleura y de la cavidad abdominal.^{4, 5} La mayoría de los mesoteliomas ocurren en personas que han trabajado con asbesto.

Neumoconiosis del Minero de Carbón

Aunque las cantidades de sílice asociadas con la minería de carbón de piedra son pequeñas, en años recientes se le ha dado importancia a esta neumoconiosis. La reacción es iniciada por depósitos peribronquiales de polvo de carbón asociado con enfisema focal. Si bien más tarde puede desarrollarse fibrosis masiva progresiva en los lóbulos superiores del pulmón, aún hay dudas que

esto ocurra sin la colaboración de una reactividad inmunológica aumentada o una enfermedad tuberculosa coexistente. Ocasionalmente pueden ocurrir las cavernas isquémicas.

El patrón radiográfico es frecuentemente nodular, pero un patrón reticular es también común. Los nódulos son menos discretos que los de silicosis y la densidad es granular. Los nódulos raras veces se calcifican. Los obreros con neumoconiosis del minero de carbón no complicada no se incapacitan ordinariamente. En contraste con la silicosis y asbestosis, la enfermedad no progresa al retirarse el individuo del ambiente polvoriento. No hay fibrosis intersticial difusa.

Otras Neumoconiosis

La beriliosis, talcosis, siderosis o siderosilicosis (polvo de hierro con sílice) deben mencionarse entre las neumoconiosis de menos prevalencia. Las medidas preventivas tomadas por las industrias, particularmente en el caso de beriliosis, han sido muy efectivas.

Enfermedades Causadas por Partículas Orgánicas

Hipersensibilidad Traqueobronquial

El espasmo bronquial asociado con sustancias generadas en la manufactura ocurre más comúnmente en personas alérgicas, pero puede suceder en personas sin historial previo de hipersensibilidad traqueobronquial. En ambientes cerrados, donde cantidades importantes de aire frío y contaminado se recirculan, las reacciones espasmódicas pueden llegar a proporciones epidémicas.

Los síntomas de hipersensibilidad traqueobronquial suelen ser inmediatos o pueden manifestarse como disnea o asma nocturna. Frecuentemente, el paciente identifica los síntomas acertadamente con condiciones ambientales en su trabajo.

El *diisocianuro de tolueno* (toluene diisocyanate) usado en la manufactura de poliuretano (polyurethane foam) es un material muy sensibilizante. El poliuretano líquido se usa para darle suavidad y brillo a materiales plásticos en la industria de muebles y para fabricar envases aisladores. Reacciones espasmódicas a esta sustancia, aún en concentraciones bajas, son severas y prolongadas; mayores concentraciones de diisocianuro de tolueno generadas en accidentes industriales han causado bronquitis asmática a bomberos y trabajadores.

El polvo fino de *antibióticos* y de *enzimas proteolíticas* generadas en la manufactura de medicinas o detergentes también puede tener como única manifestación tos severa y persistente o causar reacciones obstructivas bronquiales severas y prolongadas. La relación al trabajo de estos síntomas necesitan ser claramente identificadas.

Los obreros expuestos a grandes cantidades de *polvillo de algodón* en la industria textil pueden desarrollar un síndrome con una periodicidad característica que lleva al diagnóstico de *bisinosis*: El lunes, primer día de la semana laboral, el paciente se queja de tos seca, de disnea y fiebre ligera pocas horas después de iniciar su trabajo; ya para el segundo o tercer día de la semana desaparecen los

síntomas. A medida que pasan los meses, si la exposición periódica al polvillo de algodón continúa, los síntomas persisten a través de toda la semana. Finalmente se desarrolla una bronquitis crónica. Se teoriza que la recurrencia semanal de síntomas en la etapa inicial de *bisinosis* es el resultado de una descarga histamínica y que los síntomas persisten hasta que se agoten las reservas de histamina bronquial.

Hay otros alérgenos sutilmente escondidos en nuestro medio ambiente. El aerosol de esporas de *Aspergillus* que ocurre cuando el abanico del acondicionador de aire se pone en marcha después de un fin de semana puede causar reacciones asmáticas importantes.⁷ Las reacciones bronquiales (y tisulares) a las esporas de *actinomicetes termófilos* también ocurren al acarrear o quemar bagazo seco en nuestras centrales de caña.

Hipersensibilidad del Tejido Pulmonar

La lista de los antígenos en polvillo orgánico que causan reacción a nivel del tejido pulmonar crece todo el tiempo. La *alveolitis alérgica extrínseca* se caracteriza por: desarrollo de una reacción difusa o reticulonodular sin adenopatía hilar, anticuerpos contra la sustancia responsable en el suero, y una reacción febril con tos y disnea que ocurre de cuatro a doce horas después de exponerse al alérgeno. Aún en la etapa aguda ocurre una moderada o severa hipoxemia. Las exposiciones repetidas pueden causar una fibrosis pulmonar progresiva. No es necesario ni usual que haya un historial familiar alérgico entre los afectados.

En la *alveolitis alérgica extrínseca* la radiografía puede estar normal aún cuando se escuchan estertores y se demuestra una reducción de la capacidad vital y del flujo espiratorio. También, después de identificar una resolución radiográfica completa, una lesión restrictiva con hipoxemia puede persistir.

En el norte de los Estados Unidos de Norteamérica y en Gran Bretaña la enfermedad del granjero es la forma más común de *alveolitis alérgica extrínseca*. Esta surge a consecuencia de la inhalación de esporas de *actinomicetes termófilos* que crecen en heno húmedo. La misma variedad de hongo causa esta reacción alveolar en cultivo de setas. Esto es interés histórico para nosotros pues en el primer informe de esta alveolitis alérgica se presentó la causística de 16 cultivadores de setas puertorriqueños.⁸

Más común en nuestro medio es la reacción pulmonar a las esporas de *Termoactinomicetes vulgaris* que ocurre en trabajadores agrícolas en contacto directo con bagazo seco. Los que le echan el bagazo a las calderas en centrales azucareras, por ejemplo, están muy expuestos a desarrollar una reacción alveolar. La radiografía de pacientes con bagazosis a menudo demuestra infiltrados micronodulares que han sido confundidos con tuberculosis (Fig. 3). Si añadimos a esa radiografía un cuadro clínico de tos, fiebre, debilidad y pérdida de peso y hemoptisis raras veces, entendemos aun más claramente esta confusión. En todos estos pacientes la capacidad vital y la difusión se reducen y la hipoxemia es común. A la larga, una obstrucción moderada de las vías respiratorias también ocurre.⁹



Figura 3. Bagazosis: Presentaciones confundibles con tuberculosis.
a) Infiltrados micronodulares más prominentes en las ápices.



b) Infiltrados micronodulares difusos que imitan una diseminación miliar.

Enfermedades Causadas por Gases y Aerosoles

Los gases irritantes o líquidos aerosolizados pueden causar lesiones agudas en las vías respiratorias en el parénquima pulmonar. Diferentes partes del pulmón son lesionadas de acuerdo a la solubilidad del agente irritante, de su concentración y de la duración de la exposición a él. A veces la exposición a gases y aerosoles tóxicos es tan sutil que puede pasar inadvertida (Tabla 2).

Gases más solubles como el cloro y el amonio irritan rápidamente las vías respiratorias altas y tienden a estimular la víctima a salir del medio ambiente. En concentraciones más bajas, pero por más tiempo, como cuando no hay escape posible, estos mismos gases lastiman tanto las vías respiratorias altas, como los bronquiolos y alveolos.

Aquellos gases tóxicos menos irritantes como dióxido de nitrógeno y fosgeno pueden respirarse por más tiempo

TABLA II

Enfermedades que surgen de exposiciones limitadas (que pueden pasar inadvertidas)		
Presentación Clínica	Substancias tóxicas	Ocupaciones en (lista parcial)
Dolor de cabeza	Monóxido de carbono, solventes	Control de combustión, lavado en seco
Asma o tos seca	Formaldehida, diisocianuro de tolueno, caspa animal	Textiles, plásticos, poliuretano líquido laca, veterinaria
Edema pulmonar Pulmonía	Cloro, fosgeno, dióxido de nitrógeno, cadmio	Soldaduras, silos, laboratorios químicos y soldaduras
Sicosis	Plomo, mercurio	Garages de gasolina, fungicidas, ebanistería
Arritmias	Solventes, hidrocarburos	Limpieza de metales, reparación equipo de refrigeración
Angina	Monóxido de carbono, cloruro de metileno	Reparación de automóviles, fundiciones, ebanistería
Dolor abdominal	Plomo	Reparación de baterías, soldaduras, pintura, cerámica, plomería
Hepatitis	Viruses, tetracloruro de carbón	Laboratorios, hospitales, limpieza de instrumentos

sin causar irritación y por tanto, pueden lesionar seriamente los bronquiolos y los alveolos. De estas lesiones surgen varias presentaciones clínicas: edema pulmonar, bronquiolitis y dos destructivas lesiones reparativas- la alveolitis fibrosante y la bronquiolitis obliteradora. Es importante saber que tanto el cloro como el dióxido de nitrógeno pueden producir edema pulmonar inmediatamente después de la exposición o hasta 36 horas más tarde sin causar daño tisular irreversible. Por otra parte, el edema pulmonar o la pulmononía causada por humo conteniendo cadmio, mercurio o berilio a menudo causan daños irreversibles y frecuentemente la muerte. Cadmio puede también causar la muerte al lesionar los glomérulos y túbulos renales aún cuando una lesión pulmonar importante no ocurra.

Los bomberos o víctimas expuestas al humo en fuegos pueden desarrollar; bronquitis, bronquiolitis o edema pulmonar de origen no cardíaco. Gases tóxicos no específicamente identificados surgen de la combustión incompleta de materiales inflamables.

Discusión

En el diagnóstico de enfermedades ocupacionales del pulmón es de vital importancia la identificación del material tóxico, las circunstancias ambientales de su inhalación y el periodo de exposición. Puede ser fundamental y esclarecedor identificar exposiciones industriales previas al material bajo sospecha u otros materiales tóxicos o sensibilizantes. La ausencia o presencia de una reactividad bronquial previa puede esclarecer si la exposición industrial agravó un problema clínico establecido o lo causó. A veces la única manera de establecer una relación causal es retar el pulmón del paciente con un aerosol del agente sospechoso.

La tos y la disnea son las presentaciones clínicas más comunes. La radiografía es la forma más confiable de identificar daño tisular localizado. El patrón radiográfico ayuda en el diagnóstico. Por ejemplo, en estudios radiográficos seriados los múltiples nódulos pequeños e irregulares de silicosis simple pueden diferenciarse de la nodularidad más grande y dispersa de la neumoconiosis reumatoide.² Hay que estar muy consciente de qué reacciones tisulares sintomáticas de importancia pueden observarse, aún en la ausencia de signos clínicos.

La espirometría seriada es una manera sencilla de cuantificar limitaciones funcionales sospechadas por el historial, el examen físico o la radiografía. La espirometría puede establecer la presencia de una limitación funcional en la ausencia de cambios radiográficos. La espirometría de grupos ayuda a identificar situaciones industriales causantes de obstrucción reversible de las vías respiratorias. Estudios más detallados como gases arteriales y medidas de difusión ayudan a valorar con más precisión la disfunción fisiológica de individuos cuya espirometría señala una limitación importante.

Muchas de las enfermedades pulmonares ocupacionales están asociadas a cambios tisulares irreversibles o disfunciones pulmonares severas y persistentes. La identificación de ellas debe ser sobre todo un estímulo para modificar el ambiente o la situación de trabajo que produce la enfermedad.

El tratamiento correcto de las enfermedades ocupacionales se deriva del conocimiento de la fisiopatología existente. Las reacciones espasmódicas leves se manejan solamente con broncodilatadores. Las reacciones agudas bronquiolo-alveolares frecuentemente se benefician de corticoides en cantidades farmacológicas. Los corticoides están específicamente indicados en reacciones tardías de dióxido de nitrógeno y en el manejo de la alveolitis alérgica extrínseca donde evaluaciones clínicas espirométricas y de gases arteriales seriadas son necesarias para definir la duración óptima del tratamiento.

Abstract: The article reviews the basic principles involved in the development of occupational diseases of the lung. It describes some of the most common diseases caused by inhalation of inorganic particles (silicosis, asbestosis) of organic particles (asthma, byssinosis, bagazosis) and toxic gases (bronchiolitis, pulmonary edema). The irreversibility of pulmonary tissue destruction in silicosis and asbestosis and the need for preventive measures is emphasized. A careful occupational history, serial chest films and repeated spirometric measurements help establish an accurate diagnosis. The principles of treatment of occupational lung diseases are discussed.

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ARTICULOS ESPECIALES

"The Collection of the Boletín de la Asociación Médica de Puerto Rico and its Preservation (1903-20)"

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Summary: For the historian of the Puerto Rican medical journalism, the importance of the *Boletín de la Asociación Médica de Puerto Rico* (AMPR) lies upon its long-lasting publication, and its cultural and scientific contributions. In the previous century no medical journal lasted so much. Created in 1903 to serve as "spokesman" of the AMPR, the *Boletín* had collected the "inquietudes" and activities of the Puerto Rican physicians, as well as their precious original works. Nowadays, the AMPR lacks of a complete collection of the *Boletín*. Through a careful research conducted in several San Juan libraries it was possible to find and consult the issues that the AMPR does not have. The data collected was organized in two tables. Some volumes that belong to the first two decades are in urgent need of restoration. It is the Association's due to complete and preserve the *Boletín* collection in order to bequeath it to the future generations of doctors.

The *Boletín de la Asociación Médica de Puerto Rico* is the Puerto Rican journal with the longest lasting publication. It has subsisted almost uninterruptedly for the last eighty years.¹ The *Boletín* constitutes a landmark, not only in medical journalism but in the Island's history of contemporary journalism. No other publication of cultural importance has such as record in this century.²

There were many medical societies established in the Western Hemisphere during the XIX century. Two good examples are the American Medical Association (AMA) and the Academia de Medicina de México, founded in 1847³ and 1836,⁴ respectively. Also in 1847, a group of physicians "formed their own private medical society, the New York Academy of Medicine."⁵

Usually, these medical societies sponsored the publication of a concomitant periodical. The Journal of the AMA is celebrating this year its 100th anniversary of continuous publication. Though, the *Periódico de la Academia de Medicina de México* (sic) only lasted six years (1836-41).⁶

The establishment of the Asociación Médica de Puerto Rico had to wait until 1902 and the *Boletín* appeared on January 1903. In the previous century many medical periodicals were published here, but no one subsisted. Salvador Arana Soto compiled a list of these periodicals.⁷

Unfortunately for the researcher, copies of most of them are no longer available. Only a few titles of this list can be found at the Biblioteca Nacional - Puerta de Tierra, San Juan - and at the Puerto Rican Collection in the General Library of the Río Piedras Campus-University of Puerto Rico. For instance, one of the most interesting periodicals of that times is *La Salud*, which first year of publication, 1883, is preserved intact as a none volume-rare book at the UPR library.

A complete collection of those XIX century periodicals is nonexistent. Reasons for this are obvious: their irregular printing, short life and variable site of publication.⁸ In contrast, the *Boletín* is distinguished from these ephemeral periodicals because of its endurance and regular publication.

But to the astonishment to the historian of medicine, the *Boletín de la AMPR* is facing the risk of losing its earliest issues. There is no complete collection of the *Boletín* in any of the libraries of importance searched in San Juan. The volumes available at the Reading Room of the very AMPR, those corresponding to its first two decades, are incomplete and in a deplorable status.

In the event that the first volumes are lost, how will we know which were the ideas and "inquietudes" of the Association founders? What was the role of the native physicians, members of the AMPR, in the improvement of the public health in those crucial years? Even the texts of original research will get lost. For example, there is a

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pioneer article on medical anthropology written by Dr. Agustín Stahl that deals with the fertility of the Puerto Rican women.⁹

If we compare a recent issue of the Boletín with one of those published in its first year (1903) many differences will be evident even to the layman. Nowadays, the scientific rigorousness imposes the usage of references and footnotes, which are almost nonexistent in the original works written by physicians in the early 1900's and published in the Boletín. Obvious details are the number of pages - only sixteen in the first issue-, the quality of the paper, the quantity of advertisements and pictures, and the publication of articles written in English.

Originally, all the articles were published in Spanish, but sometimes English words were used in sentences like this one: "Proyecto para un Bill en defensa contra la uncinariasis".¹⁰ Another example is the word November instead of "noviembre" on that month's cover in 1905. The August 1912 issue stated - in English - that the Boletín was "Published monthly - under the direction of the Committee of Redaction". One of the earliest articles published totally in English, if not the first, was a reprint published on the March 1914 edition. Foreign articles and medical news were translated to Spanish by some Association members.

After an account on how the AMPR was established in 1902, reasons are given for the publication for a "vocero" to the Association:¹¹ "Se ha dado el primer paso. Ahora es preciso que el ser nacido hable, y hablará por medio de este Boletín de la Asociación Médica de Puerto Rico, que viene...a recoger (sic) para su publicación la labor profesional asilada (sic) y silenciosa hasta hoy, a poner de relieve, en suma, la cultura general del país."¹²

This article does not intend to be an analysis of the Boletín contents, but the readers may be interested to know that in the first years of its publication, this journal reflected well the two major concerns of the public health authorities: the parasitic anemia- the campaign against the *Necator americanus* - and the treatment of tuberculosis.¹³ Important articles on anemia are those written by Dr. Ashford,¹⁴ Dr. Stahl,¹⁵ and Dr. Quevedo.¹⁶ Other writings were about the establishment of the "Liga antituberculosa".¹⁷ In those years, the editors used to publish the memoranda received from the Office of the Superior Board of Health.¹⁸

The Association actively participated in an international exchange of medical periodicals. In the March 1905 issue, the following are mentioned as receiving the Boletín and sending back their own publications: the Journal of the AMA, Medical Record, Le Bulletin General de la Societe de Therapeutique de París (sic), La Revista Médica Cubana, El Boletín de la Liga contra la tuberculosis de Cuba, La revista de Medicina y Cirugía de Madrid.¹⁹ The Association members had the privilege of taking home those journals for a maximum of eight days.

In the edition for August - September 1913, the number of periodicals exchanged had increased to eighteen.²⁰ In addition to journals received from Spain, France, USA, and Cuba, new ones were from Uruguay, Colombia, El Salvador, Dominican Republic, and two from Puerto Rico itself: Boletín Oficial de la Dirección de Sanidad de P.R. and Anales Médicos de P.R.

For the historian of medicine, as well as any other person interested in the information written in the Boletín de la AMPR, it is imperative the publication of an Index of this journal. Because there is none, at least it will be useful to have a list that states where to look for a specific year or issue without major trouble.²¹ Through a careful research conducted in several libraries in the San Juan area, it was possible to find and consult the volumes that the AMPR does not have.

Table I offers a list that will help to localize the numbers published from 1903 to 1920. The four places mentioned were selected because of their availability to the serious professional, but by any means are these the only places where the volumes can be found. They are the Reading Room at the Asociación Médica de Puerto Rico (AMPR), the Puertorican Collection at the General Library of the Río Piedras Campus at the University of Puerto Rico (UPR), and two special sections at the General Library of the Recinto de Ciencias Médicas (Medical Sciences Campus of the University of Puerto Rico): The Puertorican Collection (RCM) and the Ashford Collection (AC). (See Tables I and II).

It is worthy to mention that, at the Association's Reading Room, the years 1903 to 1906 are compiled in a single volume, as the years 1907 to 1913. These volumes are in need of restoration because of their deteriorated status. Both books belonged to Dr. Luis García de Quevedo. Under the Presidency of Dr. Ramón Suárez, in 1928, they were donated to the AMPR.

TABLE I

Complete Volumes of the "Boletín are Kept at
The Following Institutions

Years	AMPR	UPR	RCM	AC
1903	X			
1904	X			
1905	X			
1906	X			X
1907	X			X
1908	X			
1909	NO ISSUE WAS PUBLISHED			
1910	X	X		
1911	X	X		
1912	X	X	X	
1913		X	X	X
1914		X	X	X
1915		X	X	
1916	X	X		
1917	X	X	X	
1918			X	
1919			X	
1920			X	

The "X" means that all the issues published that years are available; in other words, the volume is complete.

AMPR: Reading Room of the Asoc Méd de P Rico
UPR: Puertorican Collection, Gen Lib, Río Piedras Campus, University of Puerto Rico
RCM: Puertorican Collection, Gen Library, Medical Sciences Campus, Univ of P Rico
AC: Ashford Collection, Gen Lib, Med Sc Campus, Univ of P Rico

TABLE II

Incomplete Volumes of the "Boletín" are Kept at
The Following Institutions

Years	
1904	RCM
1905	RCM, AC
1906	UPR, RCM
1907	RCM
1908	UPR, RCM, AC
1909	NO ISSUE WAS PUBLISHED
1910	RCM
1911	RCM, AC
1912	AC
1913	AMPR, AC
1914	AMPR
1916	RCM

The abbreviations are explained on Table I.

When I started this research four years ago, I personally talked to the late Dr. Suárez, because it was unbelievable for me that the Association did not have a copy of all the Boletín issues. He told me that under his Presidency and initiative, a complete collection was made available for the Association members. The Association may honour the memory of Dr. Suárez, one of our most distinguished cardiologists, by following his example.

Preferably, all the collection of the Boletín should be available at the Reading Room for the Association's members benefit, even if this means to reproduce mechanically the missing volumes. This can be done using the collection available in any of the other three places previously mentioned. Maybe there are readers who own original copies of those missing volumes and would like to donate them to the Reading Room. It is a necessity to back the effort to continue the publication of the Boletín, but also to preserve the volumes that have been ignored and are at stake of becoming only a memory of the past.

The Boletín, a heritage that was left to us by the sacrifice of many, will be preserved for the benefit of present and future generations. This is an enterprise of a great responsibility. Otherwise, the XXI century Puerto Rican physicians will perceive that a complete collection of our major medical journal was denied to them because our carelessness.

I consider appropriate to close this article with the first words of the Boletín: "Es la ley del mundo que toda empresa tendiente al bien colectivo haya de encontrar en su camino dificultades sin cuento, obstáculos insuperables, antes de alcanzar su completa realización. Pero, por otra ley compensadora, ocurre que a despecho de escollos y valladares llega un momento en que aunándose circunstancias antes improbables y dándose esfuerzos imprevistos, la empresa triunfa, cuando se daba ya por imposible de realizar y cuando aparecía, sarcástica, la sonrisa en los labios de los eternos murmuradores."²²

Resumen: Para el historiador del periodismo médico puertorriqueño, la importancia del Boletín de la Asociación Médica de Puerto Rico (AMPR) estriba fundamentalmente en su larga existencia, y en su contribución cultural y cien-

tífica. Durante el pasado siglo ninguna revista médica duró tantos años. Creado en 1903 para servir de portavoz de la AMPR, el Boletín ha recogido en sus páginas las inquietudes de los médicos puertorriqueños, así como sus valiosísimas investigaciones originales. Al presente, la AMPR carece de una colección completa del Boletín. Al investigar cuidadosamente en las bibliotecas de San Juan, fue posible localizar y consultar aquellos números que no están en la AMPR. Se recogió esta data en dos tablas. Ciertos volúmenes de las primeras dos décadas ameritan urgentemente un tratamiento de restauración. Compete a la Asociación preservar y completar la colección del Boletín a fin de dejarla como un legado cultural a futuras generaciones de médicos.

Acknowledgement

I wish to acknowledge my gratitude to Juan J. Garrastegui, to whom I dedicate this article, for his insights, help, and patience.

References

1. It was discontinued after the Dec 1980 edition (No 71) and started again in Sep 1910 (No 72). Also was suspended in the Summers of 1911 and 1912 for four and three months, respectively. Under the period studied, the Boletín was published on a monthly basis, except in 1911, 1912 and 1913 when some editions were bimestral. It was a quarterly from 1915 to 1920.
2. According to Pedreira, only La Gaceta, a XIX century governmental periodical, was published almost continuously for a longer time, from c. 1806 to 1902. See Pedreira AS: El periodismo en Puerto Rico, Río Piedras, Edil, 1969:455.
3. Shryock RH: The development of modern medicine, Madison, Univ of Wisconsin Pr, 1979:110.
4. Martínez Cortés F: ¿Sirve para algo la historia de la medicina?, México, Prensa Médica Mexicana, 1981:54.
5. Rothstein WG: American physicians in the 19th century, Baltimore, Johns Hopkins Univ Pr, 1972:169. This author provides a list of the founding dates of other local and state regular medical societies before the Civil War in the USA; see pp. 237-31.
6. Martínez Cortés F: op. cit.
7. Arana Soto S: Historia del periodismo médico hasta el 1898: In (his) Los desafíos y los médicos puertorriqueños, Barcelona, Miguza, 1969:71-8.
8. Many were published at the capital, but also at Mayagüez and San Sebastián. Arana Soto, ibid.
9. For example, two lists of original papers were published in the issues of Dec 1904 (No 24) and Dec 1906 (No 49).
10. Bol Asoc Méd P Rico, Jan 1906, No 38:1.
11. The original notebook that contains the first acts of the AMPR (from 1902), is located at the Association's Reading Room.
12. Bol Asoc Méd P Rico, Jan 1903, No 1:2.
13. Fourth Annual Report of the Governor of Porto Rico, Washington, Government Printing Office, 1904:27. This report is for the fiscal year that ended in June 30, 1903.
14. Bol Asoc Méd P Rico, Dec 1903, No 12:184; Aug 1905, No 32:119-25.
15. Bol Asoc Méd P Rico, Mar 1905, No 25:36; Oct 1905, No 32:155-64.
16. Bol Asoc Méd P Rico, Sep 1903, No 9:141.
17. Bol Asoc Méd P Rico, Sep 1903, No 9:154; Nov 1906, No 48:191.
18. For instance, Bol Asoc Méd P Rico, Apr 1903, No 4:255.
19. Bol Asoc Méd P Rico, Mar 1905, No 27:49.
20. Bol Asoc Méd P Rico, Aug-Sep 1913, No 93:21.
21. Because of misprints, some issues were assigned with wrong numbers, and the mistakes were perpetuated. For example, No 87 (Dec 1912-Jan 1913) was followed by No 89 (Feb-Mar 1914), and there is no 88. The same happened to number 33. The numbers of the volumes were erroneously assigned in occasions. Compare, for instance, volumes X and XV for years 1914 and 1921, respectively. Consider that there were no interruptions. In the March 1916 issue, corresponding to year XII, it is mistakenly written "XIII". This was corrected by someone using a pencil at the AMPR.
22. Bol Asoc Méd P Rico, Jan 1903, No 1:1.



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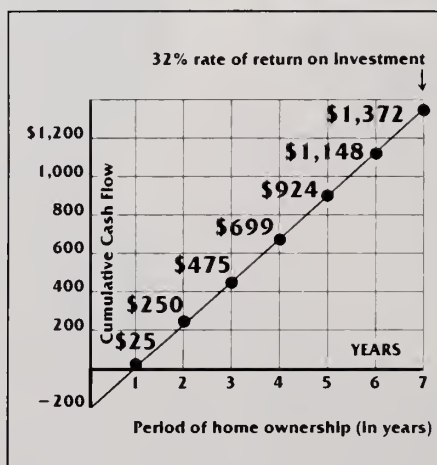
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Diagnostic Ultrasound Imaging in Pregnancy: Consensus Conference

From crude initial studies in the 1950s, ultrasonography in pregnancy has become a highly developed technology capable of detecting many fetal structural and functional abnormalities. It has found application in detecting ectopic pregnancy and multiple pregnancy, assessing fetal life and function, diagnosing physical anomalies, and guiding physicians as they make efforts to treat the fetal patient. The advent of ultrasound has overcome many of the diagnostic limitations of X-ray and has virtually eliminated the need for fetal exposure to ionizing radiation.

With these advantages and marked improvements in the technology and equipment, the use of ultrasound in obstetric practice has grown rapidly. The procedure is available in nearly all hospitals, and many physicians have acquired equipment for use in their offices. Further, because of the absence of clinically perceived risk of ultrasound and its usefulness in assessing structural anomalies, multiple pregnancy, and fetal size and gestational age, many practitioners have begun to advocate its routine use as a screening device in all pregnancies.

Lack of risk has been assumed because no adverse effects have been demonstrated clearly in humans. However, other evidence dictates that a hypothetical risk must be presumed with ultrasound. Likewise, the efficacy of many uses of ultrasound in improving the management and outcome of pregnancy also has been assumed rather than demonstrated, especially its value as a routine screening procedure.

The marked increase in the use of ultrasound, coupled with concerns regarding its safety and efficacy, prompted three NIH components—the National Institute of Child Health and Human Development (NICHD), the Office of Medical Applications of Research (OMAR), and the Division of Research Resources (DRR)—and the FDA National Center for Devices and Radiological Health to join in sponsoring a Consensus Development Conference to assess the use of diagnostic ultrasound imaging in pregnancy. The conference was held on February 6-8, 1984, after a year of preparation by the panel. After presenting a preliminary report at the conference, hearing the testimony of experts, and receiving comments and criticisms from the medical/scientific community, as well as from the public at large, the panel, consisting of physicians, basic scientists, epidemiologists, nurses,

educators, sonographers, and public representatives, considered all of the information received and provided answers to the following questions that were posed to the panel:

1. What types of ultrasound scanning are currently used in obstetric practice? How extensive is this use? What is known about the dose/exposure to the fetus and the mother from each type?
2. For what purposes is ultrasound now used in pregnancy? For each use, what is the evidence that ultrasound improves patient management and/or outcome of pregnancy?
3. What are the theoretical risks of ultrasound to the fetus and the mother? What evidence exists from animal, tissue culture, and human studies on the actual extent of the risk?
4. Based on the available evidence, what are the appropriate indications for, and limitations on, the use of ultrasound in obstetrics today?
5. What further studies are needed of efficacy and safety of use of ultrasound in pregnancy?

1. What types of ultrasound scanning are currently used in obstetric practice? How extensive is this use? What is known about the dose/exposure to the fetus and the mother from each type?

On the basis of the collective experience of members of the panel, the material presented, and the literature review that was conducted, we conclude that in obstetric practice in the United States, use of diagnostic ultrasound imaging has an expanding role, and its use is becoming widespread. Information on the extent of use of diagnostic ultrasound in pregnancy was available from single institutions and states, marketing studies, the office survey conducted by the American College of Obstetricians and Gynecologists, and the 1980 National Natality Survey. These data lead to estimates of the percentage of pregnant women exposed to at least one ultrasound examination ranging from a low of 15 percent to a high of 40 percent. There is reason to believe that all of these data sources seriously underestimate the true extent of exposure to ultrasound since they do not necessarily include exposure via Doppler devices, including those used to listen to fetal heart tones and in antepartum and intrapartum fetal heart rate monitoring.

Exposure to imaging devices in the recent past has been to static scanners, real-time equipment of the linear array type, and mechanical sector scanners. The quality used most often to report instrumentation output is intensity. Typical time average value ranges of intensity are 0.1-6 mW/cm² (spatial average, temporal average intensity) and 1-200 mW/cm² (spatial peak, temporal average

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intensity). The spatial peak, pulse average intensity typically ranges from 1-200 W/cm² for such pulsed ultrasound equipment.

The time average intensities of the typical obstetrical Doppler devices used to listen to the fetal heart and for fetal heart rate monitoring in the antepartum and intrapartum period are within the same range as for pulsed equipment. These systems operate in the continuous wave mode, viz, 0.2-20 mW/cm² (spatial average, temporal average intensity) and 0.6-80 mW/cm² (spatial peak, temporal average intensity). As new technologies and applications evolve, for example, measurement of blood flow using pulsed Doppler, exposure levels may be substantially higher.

Manufacturers of ultrasound equipment introduced into U.S. commerce are required to report outputs to the FDA. We recommend that these quantities be measured and reported to the user in a form consistent with the requirements of the AIUM/NEMA Safety Standard for Diagnostic Ultrasound Equipment.

Dose is a quantitative measure of an agent that is given or imparted and combines quantities such as intensity and exposure time. No dose quantity has been identified for ultrasound. Variation in tissue properties between individuals as well as scanning conditions influence dose in an unpredictable way. For all practical purposes, fetal dose cannot be quantitated precisely. For this reason, there are no data on the dose to either the mother or the fetus in the clinical setting. Documentation of dwell time and type of machine and transducer used would begin to address this problem. It is recommended that at least this specific exposure information be recorded for each examination. Thus, it is important that each exposure to ultrasound by all Doppler and imaging devices be recorded.

2. For what purpose is ultrasound now used in pregnancy? For each use, what is the evidence that ultrasound improves patient management and/or outcome of pregnancy?

Ultrasound has been used in a wide variety of clinical situations to aid in managing pregnancy. For each of these applications, there is literature recording the clinical experience from various centers, with evidence of benefits ultrasound has had in each respective application, although these applications have not been subjected to the rigorous evaluation provided by a randomized, controlled clinical trial. The following should not be considered circumstances in which use of diagnostic ultrasound imaging is mandatory. Rather, where significant clinical questions exist, the resolution of which would alter the remainder of prenatal care, ultrasound can be of benefit for:

- *Estimation of gestational age for patients with uncertain clinical dates, or verification of dates for patients who are to undergo scheduled elective repeat cesarean delivery, indicated induction of labor, or other elective termination of pregnancy.* Ultrasonographic confirmation of dating permits proper timing of cesarean delivery or labor induction to avoid premature delivery.

- *Evaluation of fetal growth* (e.g., when the patient has an identified etiology for uteroplacental insufficiency, such as severe preeclampsia, chronic hypertension, chronic renal disease, severe diabetes mellitus, or for other medical complications of pregnancy where fetal malnutrition, i.e., IUGR or macrosomia, is suspected). Following fetal growth permits assessment of the impact of a complicating condition on the fetus and guides pregnancy management.
- *Vaginal bleeding of undetermined etiology in pregnancy.* Ultrasound often allows determination of the source of bleeding and status of the fetus.
- *Determination of fetal presentation* when the presenting part cannot be adequately determined in labor or the fetal presentation is variable in late pregnancy. Accurate knowledge of presentation guides management of delivery.
- *Suspected multiple gestation* based upon detection of more than one fetal heartbeat pattern, or fundal height larger than expected for dates, and/or prior use of fertility drugs. Pregnancy management may be altered in multiple gestation.
- *Adjunct to amniocentesis.* Ultrasound permits guidance of the needle to avoid the placenta and fetus, to increase the chance of obtaining, amniotic fluid, and to decrease the chance of fetal loss.
- *Significant uterine size/clinical dates discrepancy.* Ultrasound permits accurate dating and detection of such conditions as oligohydramnios and polyhydramnios, as well as multiple gestation, IUGR, and anomalies.
- *Pelvic mass detected clinically.* Ultrasound can detect the location and nature of the mass and aid in diagnosis.
- *Suspected hydatidiform mole* on the basis of clinical signs of hypertension, proteinuria, and/or the presence of ovarian cysts felt on pelvic examination or failure to detect fetal heart tones with a Doppler ultrasound device after 12 weeks. Ultrasound permits accurate diagnosis and differentiation of this neoplasm from fetal death.
- *Adjunct to cervical cerclage placement.* Ultrasound aids in timing and proper placement of the cerclage for patients with incompetent cervix.
- *Suspected ectopic pregnancy* or when pregnancy occurs after tuboplasty or prior ectopic gestation. Ultrasound is a valuable diagnostic aid for this complication.
- *Adjunct to special procedures,* such as fetoscopy, intrauterine transfusion, shunt placement, *in vitro* fertilization, embryo transfer, or chorionic villi sampling. Ultrasound aids instruments guidance that increases safety of these procedures.
- *Suspected fetal death.* Rapid diagnosis enhances optimal management.
- *Suspected uterine abnormality* (e.g., clinically significant leiomyomata, or congenital structural abnormalities, such as bicornuate uterus or uterus didelphys, etc.) Serial surveillance of fetal growth and state enhances fetal outcome.
- *Intrauterine contraceptive device localization.* Ultrasound guidance facilitates removal, reducing chances

of IUD-related complications.

- *Ovarian follicle development surveillance.* This facilitates treatment of infertility.
- *Biophysical evaluation for fetal well-being* after 28 weeks of gestation. Assessment of amniotic fluid, fetal tone, body movements, breathing movements, and heart rate patterns assists in the management of high-risk pregnancies.
- *Observation of intrapartum events* (e.g., version/extraction of second twin, manual removal of placenta, etc). These procedures may be done more safely with the visualization provided by ultrasound.
- *Suspected polyhydramnios or oligohydramnios.* Confirmation of the diagnosis is permitted, as well as identification of the cause of the condition in certain pregnancies.
- *Suspected abruptio placentae.* Confirmation of diagnosis and extent assists in clinical management.
- *Adjunct to external version from breech to vertex presentation.* The visualization provided by ultrasound facilitates performance of this procedure.
- *Estimation of fetal weight and/or presentation in premature rupture of membranes and/or premature labor.* Information provided by ultrasound guides management decisions on timing and method of delivery.
- *Abnormal serum alpha-fetoprotein value* for clinical gestational age when drawn. Ultrasound provides an accurate assessment of gestational age for the AFP comparison standard and indicates several conditions (e.g., twins, anencephaly) that may cause elevated AFP values.
- *Follow up observation of identified fetal anomaly.* Ultrasound assessment of progression or lack of change assists in clinical decision making.
- *Follow up evaluation of placenta location* for identified placenta previa.
- *History of previous congenital anomaly.* Detection of recurrence may be permitted, or psychologic benefit to patients may result from reassurance of no recurrence.
- *Serial evaluation of fetal growth in multiple gestation.* Ultrasound permits recognition of discordant growth, guiding patient management and timing of delivery.
- *Evaluation of fetal condition in late registrants for prenatal care.* Accurate knowledge of gestational age assists in pregnancy management decisions for this group.

The information presented in the material reviewed by the panel, including the studies of Bennett, EikNes, Bakketeig, Grennert, and others, allowed no consensus that routine ultrasound examinations for all pregnancies improved perinatal outcome or decreased morbidity or mortality. There was, however, evidence that there was a higher rate of detection of twins and congenital malformations, as well as more accurate dating of pregnancy, but without significant evidence of improved outcome. The evidence with respect to the number of antepartum days of hospitalization and induction rates was contradictory among trials. The data on perinatal outcome were inconclusive. The panel recognized the inadequacy of the

clinical trials on which these conclusions are drawn. Furthermore, it is acutely aware of the difficulty associated with conducting ideally controlled clinical trials and the large numbers of patients that must be included to uncover differences between control and experimental groups, where a morbid event occurs infrequently and spontaneously in the control population.

The panel concludes that diagnostic ultrasound for pregnant women improves patient management and pregnancy outcome when there is an accepted medical indication. Randomized, controlled clinical trials would be the best way in the United States to determine the efficacy of routine screening of all pregnancies.

3. What are the theoretical risks of ultrasound to the fetus and the mother? What evidence exists from animal, tissue culture, and human studies on the actual extent of the risk?

The panel conducted an extensive review of the primary literature on this subject and of reports by the Bureau of Radiological Health (1976), Food and Drug Administration (1982), World Health Organization (1982), and the National Council on Radiation Protection and Measurements (1984).

A number of epidemiological studies tend to support the safety of diagnostic ultrasound exposure in humans. In particular, in the three randomized clinical trials in which half of the women were exposed routinely to ultrasound, there was no association of routine ultrasound exposure with birth weight. In the two studies that addressed the subject, no association of ultrasound exposure with hearing loss was observed. On the other hand, many of the studies reporting on the safety of diagnostic ultrasound in humans were considered inadequate to address many other important issues because of technical problems in conducting such research.

Some of the more than 35 published animal studies suggest that *in utero* ultrasound exposure can affect prenatal growth. When teratological effects have been found, energies capable of causing significant hyperthermia have usually existed.

A number of biological effects have been observed following ultrasound exposure in various experimental systems. These include reduction in immune response, change in sister chromatid exchange frequencies, cell death, change in cell membrane functions, degradation of macromolecules, free radical formation, and reduced cell reproductive potential. It should be noted that (a) some of the studies employed energy levels greater than would be expected to exist in clinical use; (b) *in vitro* exposure conditions to ultrasound used in many of the experiments are hard to place in perspective for risk assessment; (c) some of the observations, for example, sister chromatid exchange frequency changes and induction of chromosomal abnormalities, have not been reproducible, tending to refute the original findings. Nevertheless, some of the reported effects cannot be ignored or overlooked and deserve further study as outlined in our answer to Question 5. The existence of these studies is one

of the factors that contributed to our decision that routine ultrasound screening cannot be recommended at this time.

4. Based on the available evidence, what are the appropriate indications for, and the limitations on, use of ultrasound in obstetrics today?

From the body of information reviewed, taking into account the available bioeffects literature, data on clinical efficacy, and with concern for psychosocial, economic, and legal/ethical issues, it is the consensus of the panel that ultrasound examination in pregnancy should be performed for a specific medical indication. The data on clinical efficacy and safety do not allow a recommendation for routine screening at this time.

Ultrasound examinations performed solely to satisfy the family's desire to know the fetal sex, to view the fetus, or to obtain a picture of the fetus should be discouraged. In addition, visualization of the fetus solely for educational or commercial demonstrations without medical benefit to the patient should not be performed.

Prior to an ultrasound examination, patients should be informed of the clinical indication for ultrasound, specific benefit, potential risk, and alternatives, if any. In addition, the patient should be supplied with information about the exposure time and intensity, if requested. A written form may expedite this process in some cases. Patient access to educational materials regarding ultrasound is strongly encouraged. All setting in which these examinations are conducted should assure patient's dignity and privacy.

Given that the full potential of diagnostic ultrasound imaging is critically dependent on examiner training and experience, the panel recommends minimum training requirements and uniform credentialing for all physicians and sonographers performing ultrasound examinations. All health care providers who use this modality should demonstrate adequate knowledge of the basic physical principles of ultrasound, equipment, recordkeeping requirements, indications and safety.

5. What further studies are needed of efficacy and safety of use of ultrasound in pregnancy?

It is critical, in view of the existing data and the special considerations affecting fetal and embryonic development, to encourage and support a sustained research effort aimed specifically at test systems that can help provide a better data base for developing reasonable estimates of bioeffects and of risk. In particular, we recommend:

1. The study of fundamental mechanisms leading to bioeffects.
2. Laboratory experiments that focus especially on those cellular processes that are most likely to be affected during embryonic and fetal development.
3. Postnatal studies in animals after in utero exposure to ultrasound.
4. Exploration of interactions between administered ultrasound and such developmentally significant agents as drugs, nutrition, ionizing radiation,

hyperthermia, and hypoxia.

5. Development of improved dosimetry.

A long-term followup of infants involved in a randomized clinical trial would help clarify questions about the effect of ultrasound on development in humans, and other epidemiologic studies using a wide variety of methods should be considered. Studies of the psychosocial, ethical, and legal aspects of ultrasound use are also needed.

Further nonexperimental studies that seek to establish the clinical efficacy of ultrasound should address the question of its contribution to reducing morbidity and mortality. Randomized, controlled clinical trials of routine ultrasound screening in pregnancy should be conducted in the United States.

Members of the Consensus Development Panel were:

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Bartolomei Aguilera, Victoria, MD - Universidad de Puerto Rico, 1978, Oftalmología. Ejerce en Hato Rey.

Canales Quintero, Carlos A., MD - Universidad Zaragoza, España, 1978, Medicina General. Ejerce en Hato Rey.

Capella Hernández, Antonio, MD - Universidad de Puerto Rico, 1978, Medicina de Familia. Ejerce en Caguas.

Carazo Rodríguez, Brenda S., MD - Universidad del Caribe, Cayey, Diciembre 1980, Medicina Interna. Ejerce en Caguas.

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Nota Editorial:

A petición de la Dra. Zaida E. Quiles-Paredes su especialidad debe leer Medicina General y no Medicina Interna como apareció en la Sección de Socios Nuevos del mes de julio de 1984 (76:327)

La Junta Editora pide disculpas a la Dra. Quiles por este error de redacción.

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MEDICAL ASPECTS OF NUTRITION

Behavior and Nutrition: A Mini Review*

Judith L. Rapoport, M.D.**
Markus J.P. Kruesi, M.D.**

Convictions abound about behavioral effects of foods and nutrients and do indeed influence the diets of individuals as well as society.^{1, 2, 3} What scientific evidence is there to support or refute the ubiquitous and powerful beliefs about nutritional influences upon behavior?

Well-recognized gross effects of diet, such as the relationship between low blood sugar and loss of consciousness, are not covered in this article. Similarly, studies of starvation and/or protein-calorie malnutrition effects upon behavior are beyond the scope of this mini review.^{4, 5} The controversy concerning "food allergy" as a cause of behavioral symptoms has recently been reported elsewhere and also is not included.⁶

A crucial issue in most studies of the behavioral effects of foods is double blind testing: Did either the subjects or the examiners know who received which food or nutrient or when?

Sugar and Hyperactivity

Some animal experiments have suggested causal relationships between diet and activity. For example, when rats were placed on diets where the ratio of carbohydrate to protein was systematically increased, but calories kept constant, their motor activity increased proportionately.⁷

A recent study found significant correlations between carbohydrate/protein ratio with directly observed aggressive and restless behavior in a sample of 28 hyperactive children.⁸ An estimation of sugar intake based upon large categories of food also was associated with the same behaviors in the hyperactive group. Among the normal control children, dietary carbohydrate/protein correla-

ted only with restless behavior. However, the study did not prove that sugar caused hyperactivity or aggressivity; there were only correlations between those behaviors and carbohydrate/protein ratios and estimations of sugar intake. It could be that active or aggressive children simply may crave, demand or get more sugar.

One way to study causal effects is a challenge study. Two investigators have carried out such studies. At National Institutes of Health (NIH), 21 children, whose families had responded to an advertisement seeking children with adverse behavior patterns supposedly worsened following sugar, were studied as they received challenges of sucrose, glucose or a sweet-tasting placebo.⁹

By adding saccharin to all three challenges, and administering the substances as a lemon-flavored ice slurry, a double blind study was maintained. This study found none of the behavioral changes that had been reported by mothers. Furthermore, children with no psychiatric diagnosis, as well as those with one or more psychiatric diagnoses, were found to be significantly less active on sugar than on placebo.

In contrast, at Children's Hospital in Washington, D.C., investigators gave regular orange juice (the control), or juice sweetened with sucrose or fructose, to 13 psychiatrically ill children.¹⁰ The children showed an increase in total movement for each sugar compared to control.

Given the small amount of good scientific data, it is premature to reach a conclusion regarding the presence or absence of a relationship between sugar and hyperactivity.

Breakfast and School Performance

The powerful effect that public perception of nutrition/behavior relationships can have prior to good scientific evidence (for a particular opinion) is exemplified by an analysis of the school performance benefits of the United States school feeding program.² The idea that children do better in school if they have had a good breakfast, as opposed to none, is not apt to generate

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**National Institute of Mental Health, 9000 Rockville Pike, Bethesda, Maryland 20205

much controversy. Early studies on the impact of breakfast and performance indicate that a relationship between good nutrition and a child's capacity to learn influenced public policy to the extent that it became law in The Child Nutrition Act of 1966 (PL80-642).

This law expanded the National School Lunch Program to include breakfast as well as a myriad of other programs. However, 12 years later, Pollitt reviewed evaluations of the school breakfast program and concluded that further research is needed to evaluate the impact of breakfast by well-controlled design and defined measures of performance.

Subsequently, two studies that were well-controlled, support the idea that skipping breakfast impaired children's late morning, problem-solving performance.^{11, 12} On the matching familiar figures test (which has some correlation with educational achievement), there was a significant increase in the number of errors when breakfast was skipped. Similarly, another recent investigation of breakfast versus no breakfast in children showed poorer performance, both on a continuous performance task and on an arithmetic task without breakfast, although the time course of these effects differed.¹³

Caffeine and Behavior

To understand the behavioral effects of various nutrients, the better studies have been very selective, isolating one substance at a time for the study. Thus, rather than look at diet in the form of all versus none (e.g., fasting versus breakfast), another strategy involves looking at the effects of specific food substances. Of these, caffeine has been the most well-studied.

Early studies of caffeine's effect on behavior were summarized in 1962.¹⁴ The most consistent findings were that caffeine counteracts fatigue (measured with simple vigilance tasks).

Recently, in a study of grade-school children, it was shown that single doses of caffeine, given in a placebo-controlled study, produced increased vigilance and decreased reaction time, a pattern similar to that in adults.¹⁵ Moreover, high doses of caffeine (10mg/kg) produced increased motor activity. The most interesting, *newer* observation in both children and earlier studies with adults is that the amount of caffeine a person habitually selects in the diet very important in predicting the effects of this stimulant.^{16, 17, 18} Caffeine effects may differ for low and high users, perhaps in part because of baseline behavioral and autonomic differences between low and high intake groups. Studies of adults showed that caffeine may produce adverse effects, including headache, irritability and insomnia, especially in people who usually avoid caffeine.^{17, 18} However, habitual high caffeine consumers may experience positive effects.

One study involving high and low caffeine-consuming children provides some significant comparisons: High intake consumers were more likely to report that they were "nervous" or "got mad easily".¹⁶ Their parents reported that they were "more easily frustrated" and that their "demands must be met immediately." Since the groups had been off caffeine for only 24 hours at the time the above assessments were made, the possible caffeine

withdrawal effects could not definitely be differentiated from the level of intakes by different groups.

However, a preliminary study again demonstrated behavioral differences between children from the two extremes of caffeine consumption when off caffeine for two weeks. Since these groups were without caffeine for two weeks, these are not withdrawal effects, but true differences in the groups who choose different amounts of caffeine. A total of 800 grade-school children, male and female, were surveyed for caffeine intake during a 24 hour period. Twenty of the top 30 children and an age/sex/classroom-matched control, who reported low caffeine consumption, agreed to be in the challenge study at the National Institute of Mental Health (NIMH).

High caffeine consumers were more likely than low caffeine consumers to be rated hyperactive by their teachers ($p < .001$). One third of the high caffeine consuming group (9 of 30) would be considered clinically "hyperactive" compared with none of the low caffeine consumers. High and low groups did not differ in their reported side effects or their academic scores.

Caffeine effects also vary among personality types. Experiments have shown that low impulsives, as measured by a personality inventory, are hindered in performing tasks like those found on the verbal section of the Graduate Record Exam by drinking caffeine in the morning.¹⁹ Conversely, high impulsives were helped. When the caffeine and test were administered in the evening, the pattern seen was reversed.

Diet and Criminality

Studies of diet and criminality, like most other studies of behavioral effects of foods and nutrients, are not well done. Thus, there is minimal data to support the theory that diet influences criminality.²⁰ One of the best studies to date found that more insulin was secreted during glucose tolerance testing among antisocial men with aggressive conduct compared to men in the same institution who were *not* aggressive.²¹

This study does not indicate a cause and effect relationship between antisocial behavior and insulin hypersecretion and, like the study of the diets of hyperactive children (who as a group may become delinquent later), only a correlation was found.

If this work were replicated, however, it would point the way to interesting future research, i.e.: Do violent criminals self-select a different diet because they are metabolically different from other persons? Would dietary change improve their behavior? Such speculations must be tested with larger groups, using precise definitions of the dietary change conducted in randomized double blind trials with valid behavioral measures.

Summary: The finding that there is an effect upon measurements relevant to school performance, depending on whether or not the child had breakfast that morning, may seem trivial and like common sense to any parent who has had to remind their child not to leave for school without breakfast. Yet, it is an example of a hypothesis finally being tested. Caffeine in children and adults tends to increase vigilance. Differences in caffeine effects are seen among different personality types and among those who self-select

high or low amounts of the stimulant in their diets. There is no clear behavioral toxicity from caffeine in normal children. Those self-selecting high caffeine diets generally do not seem to get negative effects.

Whether most other beliefs about behavioral effects of foods and nutrients are facts or myths still needs to be determined. Until adequate scientific evidence is collected, individual beliefs about sugar, hyperactivity and crime must remain only beliefs, regardless of how strongly public policy may or may not endorse them. At this time, there is no proven causal relationship. More studies with adequate design details are needed to assess behavioral toxicity as well as the benefit/risk ratio of any dietary manipulation.

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SIRVIENDO AL PUEBLO Y A LA PROFESION MEDICA



ASOCIACION MEDICA DE PUERTO RICO

Pica During Pregnancy*

Carolyn J. Lackey, Ph.D., R.D.*

Food cravings are an accepted phenomenon of pregnancy. Pickles and ice cream spark an immediate word association with pregnancy. Cravings of some women, however, go beyond boundaries of culturally accepted food substances.

Pregnant women's cravings for dirt, clay and a host of other nonfood items is often viewed as an abnormal practice. Pregnant women have engaged in this practice, called pica, for centuries. While considered bizarre in most developed countries, it is fostered in some developing countries and viewed as a normal course of pregnancy.

Current nutrition and medical texts provide little discussion. One might interpret this lack of attention to mean pica is of historical significance only. However, omission of the subject more often indicates lack of awareness rather than the total demise of the practice.

Definition

Pica denotes the compulsion for persistent ingestion of unsuitable substances having little or no nutritional value. Pregnant women are identified as one subgroup of pica practitioners. Craved substances may be the more commonly reported dirt and clay (geophagia) or starch (amylophagia). Less frequently reported substances include burnt matches, charcoal, soot, toilet bowl air-freshener, cigarette ashes, baking soda, coffee grounds and tire inner tubes. No substance seems to be immune from a pica craver's imagination.

Cooper and Laufer provided surveys of pica from the sixth through the early twentieth century.^{1, 2} One concludes that pica is not limited to any one geographic area, time, race, creed, culture, sex or status within a culture.

Pica Hypotheses

Hypotheses for pica causation range from disease to custom explanations.^{3, 4, 5}

These theories include explanation as a *psychological phenomena* where the craving is a response to a need that has no physiological basis. The stimulus is considered psychological and is the female's response to the pregnancy state.

A *cultural basis* was often referred to in early explanations of pica. The stimulus for clay and dirt ingestion may be associated with women's early roles as gardeners and potters, which placed them in a position where consumption of surrounding clay was "normal." Identity

with the female community passed the tradition along and desire to conform to cultural mores of some developing countries may have sustained the practice.

Another cultural link suggested was eating of dirt and clay as a physical connection with the lost homeland for refugee peoples. Or, clay eating may have been adopted by West Africans in an attempt to avoid slave markets since some slave traders rejected this as an unhealthy practice that resulted in sickness.

Use of pica substances to relieve nausea, hunger or appease the appetite in some manner is the basis of the *sensory theory*. Nonfood substances may have been chosen when food supplies were scarce. Coping with other sensory manifestations, such as altered taste or smell or increased salivation, are cited as *physiological reasons* for pica.

One of the earliest explanations for pica was that cravings resulted from the body's instinctive search for inadequate nutrients. Thus, pica was a manifestation of *nutritional needs* with the body interpreting and acting upon the altered needs during pregnancy.

A more recent theory for clay consumption is suggested by its reaction in a *microbiological* medium. Clay in the intestine may promote a pH favorable to growth of microflora that counteracts growth of harmful microorganisms. Or, clay eating may relieve intestinal spasms by absorbing excess gastric secretions that are stimulated by worm infestation.⁴ Knowledge of these effects of clay eating may have given pica a place in folk medicine practices.

No one theory has emerged that can stand the test of the various types of pica cravings, particularly in addressing pica in affluent countries. Pica is probably shaded by both cultural and physiological bases.

Nutritional Concerns of Pica Practice

Several mechanisms of pica's adverse effects on nutritional and medical status have been proposed.⁶

First, the pica substance may displace other foods, thus leading to calorie and/or nutrient malnourishment.

Second, the pica substance may provide calories (i.e., starch) and result in undesirable weight gain if total calories are not compensated.

Third, the ingested substance may be toxic or contain nutrients not tolerated by individuals in certain disease states.

Also, the pica substance may have a cation exchange capacity, thus reducing absorption of essential nutrients. And, intestinal blockage or bowel perforation may result from a pica substance. Thus, potential for nutritional impact depends upon the type and quantity of pica substance ingested. There is a need for additional study to determine if there is an impact on other nutrients in the food supply.

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Iron Deficiency/Anemia and Pica

Pica has been posed as being a cause of, a result of, or having no relationship to iron deficiency/anemia. Using incidence data for iron deficiency/anemia in pregnant women, with and without pica, some researchers support pica as a causal agent for these nutritional deficiencies.^{7, 8, 9} Others, comparing data on iron deficiency/anemia and pica incidence, did not find statistically significant associations. However, in most cases, hemoglobin levels and iron/RBC ratios were lower and/or toxemia incidence was higher for pica practitioners than for controls.^{10, 11, 12} Others hypothesized that a difference in dietary practices of females, with and without pica, linked pica and iron deficiency/anemia.^{13, 14}

Several attempts have been made to link clay or starch ingestion directly with impaired iron absorption. Reduced iron absorption for starch eaters has been reported.¹⁵ A case of severe anemia and hypokalemia was associated with mineral binding from consumption of large quantities of clay.⁹ However, others were unable to show impaired iron absorption in the presence of clay or starch ingestion.¹⁶

It also has been suggested that nutrient displacement from reduced consumption of foods, when a pica substance was consumed, was the reason for iron deficiency/anemia instead of mineral binding.

Other Medical Complications of Pica in Pregnancy

Reports are available of toxicity and physical complications associated with pica. A full-term asymptomatic child was born with congenital lead poisoning secondary to maternal pica for wall plaster.¹⁷ Hemolytic anemia has been reported secondary to maternal ingestion of mothballs and toilet bowl air freshener.^{18, 19}

One female in the 33rd week of gestation was thought to be in premature labor, but the diagnosis was later changed when a clay-containing fecal impaction was discovered as the cause of the acutely tender and irritable uterus.²⁰

In another case of fecal impaction, labor subsided until the clay containing intestinal obstruction was alleviated with enemas.²¹

Clay and Starch-Eating Specifics

- *Clay.* Ill effects of prolonged eating of clay or dirt were reported in the early 1900s and coined *cachexia africana*. These ill effects were later recognized as a potassium deficiency. Tropical regions seemed more predisposed than other climates to *cachexia africana*. And, poor nutrition was often a concomitant problem.

Perhaps the highest U.S. incidence of clay and dirt eating reported anywhere is for the southern U.S. black population. This may reflect a sampling bias since random sampling of all U.S. population groups was not performed. Suggested origins for the practice include adoption by acculturation from American Indians and migration of the practice from Africa with the slave trade. Poverty and poor nutrition may have favored adoption and perpetuation of the practice.

The manner of handling clays and types preferred varies widely. Red clays are prized by some, while white or yellow clays are selected in other areas. Clay may be eaten in lump form as it comes directly from the earth or receive minor treatment by drying or more elaborate preparation by molding in shapes of bricks, baskets, tablets or figurines. Salt and/or vinegar may be added prior to baking.

Clays are extracted from exposed banks as well as clay pits several feet deep. White clays are described as creamy and sweet and red clays as gritty and tart. Clay eaters attribute taste and texture differences as important distinguishing factors.

Clay eaters report daily consumption of a lump or two of clay to one quart or more of clay. Average consumption of 30 to 50 grams has been reported. Incidence of clay eating in the U.S. varies with a high of 50% to lows of 27%, 10% and 9% of those pregnant women being surveyed. However, no surveys have been conducted on a total U.S. population basis to determine pica incidence during pregnancy.^{14, 22, 23, 10}

Clays have been analyzed for both mineral content and cation binding capacities. Potassium content varies greatly with type of clay evaluated.^{24, 25} Hunter's analyses for 11 elements resulted in wide variations in mineral values.³

- *Starch.* Starch eating is often explained as the commercial substitute for clay. When local clay became unavailable through migration from clay-containing U.S. southern homeland, laundry starch was substituted. Starch eaters have indicated that clays are unclean and commercial packaged products are more sanitary.

Unlike clay, starch has a very definite impact on nutritional status since it supplies about 1600 Kcal per pound. Consumption levels range from a handful to several boxes a day. The lump/dry laundry starch is eaten without any further preparation. The dry starch "squeaks" in the mouth. Reports of starch eating incidence vary with 41%, 75%, 35%, 46%, 24%, 18%, 17%, and 10% of those pregnant women populations being surveyed.^{22, 14, 12, 10, 7, 26, 27, 23}

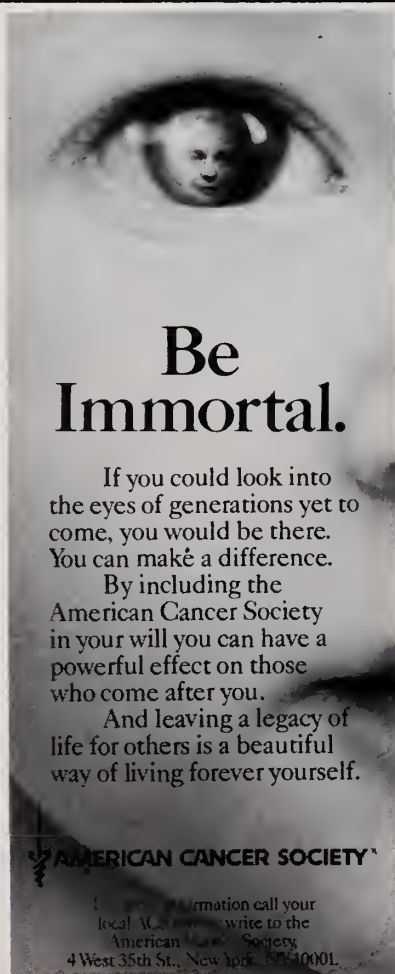
Summary: Pica during pregnancy has been noted for centuries. When discussed it is often assumed that pica is no longer practiced in developed countries. However, the small number of incidence surveys of the past 15 years suggest that pica is still being practiced.

Information on current incidence and types of pica is lacking. Questions on pica are not routinely included as a part of prenatal care sessions.

Pregnant women need to be questioned about their food cravings and pica specifically. Damaging medical and nutritional impacts from pica substance ingestion need to be considered and researched. We know little more about the cause(s) of pica during pregnancy today than did the early explorers who reported on this behavior.

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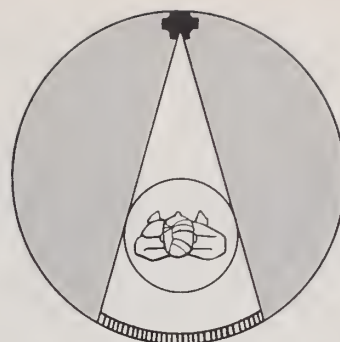
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CT Diagnosis



Heriberto Pagán-Saez, MD.*

CASE PRESENTATION

This is a 6 years old female with history of a CVA in 1983, and comes to the clinic with a left hemiparesis. A CT of the brain revealed the changes shown in figures 1 and 2.

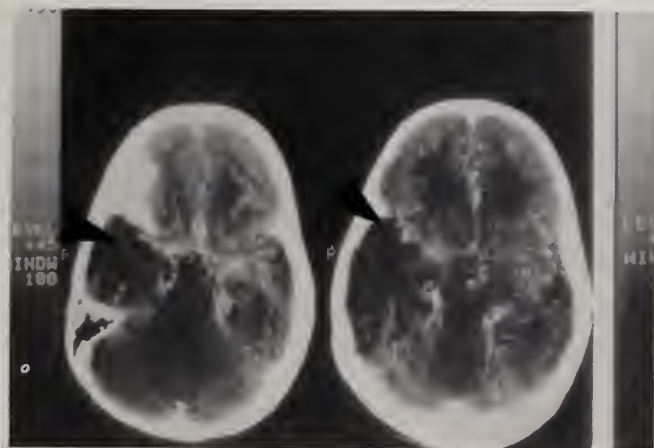


Figure 1: Ill defined main intracerebral arterial branches associated with irregular low density areas involving the right temporal lobe with abrupt tapering of the R-MCA horizontal segment (see arrow).



Figure 2: Shows a low density area involving the territory of the R-MCA with no significant contralateral shift of the mid line structures. (see arrows)

*Director Department of Radiological Sciences University of Puerto Rico, Medical Sciences Campus.

A right carotid arteriography showed occlusion of the R-MCA (right middle cerebral artery) with associated massive collateralization through the lenticulo striate arterial bed (see double arrows in Figure 3 and Figure 4).



Figure 3

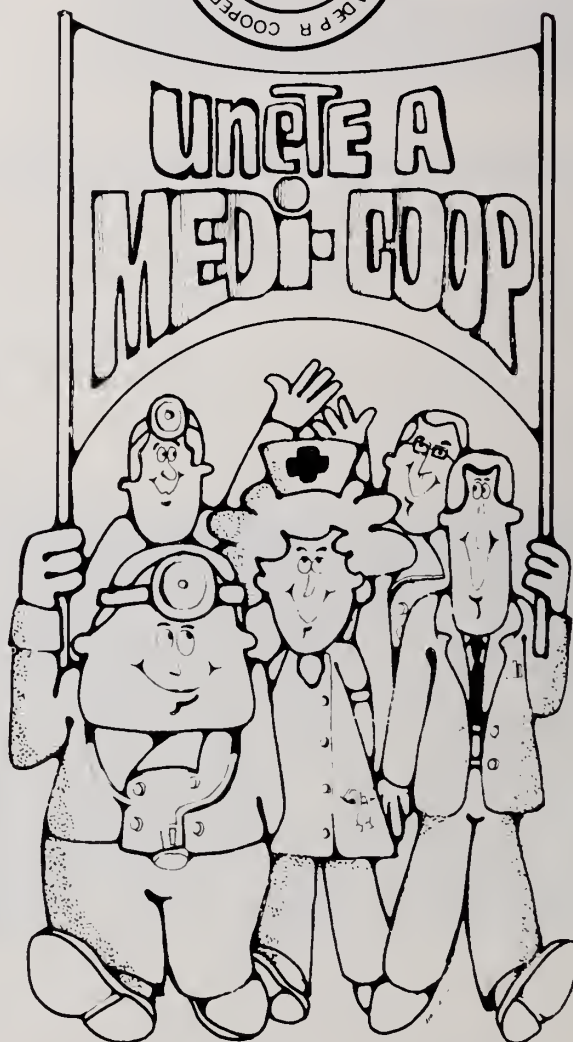


Figure 4

Diagnosis: Moya - Moya Syndrome (Bilateral Occlusive Disease of the carotid arteries)

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What can you do for hypertensives like Paul H?

Newly diagnosed

At 39, annual physical uncovered mild disease with a diastolic of 94 mmHg.

Heavy smoker

Two packs a day. "Might consider" hypnosis when he decides to quit.

Obsessive

Has rigid habits. Will have difficulty coping with a complicated regimen.

Physically inactive

Hates exercise and heavy business lunches aren't helping his weight.

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Paul H represents 2,514 men under 40 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Paul H's age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol may produce bronchial hyperactivity in patients with no history of asthma.³ Reasons for this are not fully understood, but smoking has been implicated⁴—especially in males like Paul H. TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Paul H...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN® (atenolol)

For Paul H...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-(1-methylethyl) amino] propoxy]-. Atenolol (tree base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyroidosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Resúmenes de La Literatura Médica

PRIMARY SURGICAL CLOSURE OF VENTRICULAR SEPTAL DEFECT IN THE FIRST YEAR OF LIFE: RESULTS IN 128 INFANTS.

Yeager SB, Freed MD, Keane JF, et al. J Am Coll
Cardiol 1984; 3:1269-1276

Los autores de los departamentos de Pediatría y Cirugía Cardiovascular del Hospital de Niños de Boston reportan su experiencia de 8 1/2 años con la reparación quirúrgica de las comunicaciones interventriculares (CIV) en el primer año de vida.

Las indicaciones para cirugía fueron: insuficiencia cardíaca, retraso del desarrollo somático, o hipertensión arterial. Las complicaciones posoperatorias fueron bloqueo completo de la rama derecha (64%); bloqueo bifascicular (9%); cortocircuitos residuales significativos (6.2%); trastornos neurológicos transitorios (3.9%) y bloqueo AV completo persistente (2.3%). La presión pulmonar pos operatoria se normalizó en todos los casos re-estudiados excepto en dos con cortocircuito residual significativo.

La mortalidad hospitalaria fue de 7.8% y la tardía 2.3%. La mortalidad fue mayor en los más jóvenes con problemas respiratorios pre-existentes o con cortocircuitos residuales pos operatorios hemodinámicamente significativos.

Las implicaciones de este estudio son:

- que el cierre quirúrgico de las CIV en el primer año de vida representa una alternativa eficaz para la mayoría de estos infantes sintomático.
- que en aquellos con cortocircuitos residuales hemodinámicamente significativos la mortalidad es mayor
- que la reparación temprana de las CIV evitan alteraciones irreversibles de la vascularidad pulmonar
- que la incidencia de bloqueo AV completo así como el bloqueo completo de rama derecha pos operatorios no es mayor que en los niños más grandes
- que la cirugía exitosa en este primer año de vida puede resultar en un crecimiento y desarrollo normales en la niñez.

Rafael Villavicencio, M.D., FACC

COMBINED DISCRETE SUBAORTIC STENOSIS AND VENTRICULAR SEPTAL DEFECT IN INFANTS AND CHILDREN. Chung KJ, Fulton DR, Kreidberg MB, et al. Am J Cardiol 1984; 53:1429-1432.

La estenosis subaórtica discreta (ESAD) constituye el 10% de las estenosis aórticas congénitas. Consiste de una membrana o un saliente fibroso en el tracto de salida ventricular izquierdo inmediatamente debajo de la válvula aórtica. Suele acompañarse de otros defectos, casi siempre comunicación interventricular (CIV), conducto arterioso patente (PDA), y coartación de la aorta. Su diagnóstico puede lograrse mediante ecocardiografía bidimensional lo cual permite su resección quirúrgica eliminando la obstrucción ventricular izquierda.

Los autores, de los Departamentos de Pediatría y Cirugía del Hospital Universitario de Tufts, en Boston informaran de su experiencia en 8 casos con ESAD y CIV. Los estudios iniciales incluyendo ventriculografía izquierda y ecocardiografía demostraron otros defectos asociados incluyendo coartación de aorta y PDA pero ninguno tenía evidencia de ESAD. Seis casos requirieron tratamiento quirúrgico y en ninguno hubo que cerrar la CIV. En los ecocardiogramas 2-D de seguimiento pos operatorio se evidenció cierre espontáneo de la CIV (6 de ellos con formación de aneurisma del septo) y luego la aparición de la membrana sub-aórtica con una válvula aórtica normal. En todos los casos hubo un gradiente significativo (35-116 mm Hg) siendo \geq 50 mm Hg en 6 de ellos. En todos se practicó la resección quirúrgica de la membrana y en ninguno hubo evidencia de obstrucción residual post operatoria del tracto de salida izquierdo.

El estudio indica que la ESAD se asocia frecuentemente a CIV pequeñas, especialmente aquellas que cierran formando aneurismas en la porción membranosa del septo interventricular. La ESAD puede no estar presente en la evaluación inicial. Dado el carácter progresivo de la ESAD luego del cierre espontáneo de las CIV, es necesario tener esta alternativa en mente, sobre todo si persiste un soplo significativo y un electrocardiograma anormal. El ecocardiograma bidimensional esta indicado en el seguimiento de estos casos para lograr el diagnóstico preciso y llevar a cabo el tratamiento adecuado.

Rafael Villavicencio, M.D., FACC

DURATION OF MIDDLE EAR EFFUSION AFTER ACUTE OTITIS MEDIA. Schwartz RH, Rodriguez WJ, Grundfast KM. Pediatric Infectious Disease. 1984; 3:204-207.

Se estudiaron 76 niños de 3 meses a 3 años de edad, blancos de clase media. El criterio para entrar en el estudio fue otitis media con efusión persistente (OMP) después de 10 días de tratamiento con amoxicilina. La evaluación consistió en otoscopia, neumatoscopia, en algunos casos timpanogramas y cuando estaba indicada, la miringotomía. Otro grupo de 45 niños saludables sin otitis fue evaluado a modo de grupo testigo. El seguimiento se hizo a los 10 días inicialmente, luego cada 14 días y, ulteriormente cada 30 días hasta completar 6 meses. Los autores calculan que la otitis media con efusión persiste inicialmente en el 50% de los casos. Después de los primeros 10 días se encuentra la OMP en el 29% de los casos un mes más tarde; en el 14% a los dos meses y en el 6% después de los tres meses. Esta cifra aumenta si se incluyen el la casuística otros 4 niños que se excluyeron del estudio después de haber sido admitidos en el mismo, porque se les practicó la timpanostomía para la inserción de tubos. Si se incluyen estos la cifra de OMP después de los tres meses sería de 12%. Se encontró que incluyendo los casos de timpanostomía, había una correlación entre historia previa de más de tres episodios de otitis previa y una mayor propensión a la OMP. En 38 de los niños con OMP a los 10 días del tratamiento inicial se administró un curso de dos semanas de trimetoprim-sulfametoxazol, pero al compararse este grupo con los que no recibieron el tratamiento adicional no hubo diferencia en la OMP durante la observación ulterior. La miringotomía se hizo en 8 casos. Los autores señalan que se necesitan estudios más amplios para valorar el efecto del procedimiento.

Se concluye que en la mayoría de los casos la otitis media con efusión persistente es una afección autolimitada y que las visitas de seguimiento en estos casos pueden realizarse a intervalos de 4 a 6 semanas. Se recomienda como parte del seguimiento la neumatoscopia o el timpanograma o ambos. Se describe la neumatoscopia como un arte que guarda estrecha relación, cuando demuestra inmovilidad de la membrana, con la curva plana, tipo B, del timpanograma.

José E. Sifontes, M.D., FAAP

FOOD HYPERSENSITIVITY. Metcalfe DD. J Allergy Clin Immunol 1984; 73:749-762

La valoración de la hipersensibilidad o alergia alimentaria es uno de los problemas más difíciles de la práctica de la alergia e inmunología. Se calcula que sucede entre 0.3 y 7.5% de las personas y es más común en los niños de menor edad. La mayoría de las reacciones alérgicas a los alimentos están mediadas por la inmunoglobulina E que reacciona con los alérgenos y conduce a la liberación de los mediadores químicos de las células cebadas; y éstas abundan en el intestino. Las reacciones pueden además

estar mediadas por anafilatoxinas derivadas de complemento y por interacciones de este con las inmunoglobulinas M y G. A veces las células cebadas liberan los mediadores como reacción a un fármaco como la codeína.

Los síntomas son digestivos, respiratorios (asma), cutáneos u otros inespecíficos y no comprobados sin lugar a dudas, tales como cefalea, cansancio, depresión.

Los alimentos de ciertos grupos botánicos relacionados pueden causar reacciones alérgicas cruzadas; por ejemplo entre ostras, almejas, cebada y maíz, canela y laurel. Los preservativos añadidos a los alimentos o bebidas pueden causar reacciones aparentemente alérgicas particularmente la tartracina (amarillo FDA # 5) que está relacionada con la reacción a la aspirina, y los bisulfitos que se usan ampliamente como preservativos de alimentos en los restaurantes, comidas y bebidas. El diagnóstico y a la vez el tratamiento de las reacciones a los alimentos y bebidas consiste en las dietas de eliminación. La inmunoterapia y la hiposensibilización oral no se recomiendan. La alergia alimenticia que aparecen antes de los años de edad suelen aliviarse después de la infancia; no así las que se manifiestan después de los tres años de edad. En los casos de anafilaxis por un alimento, además del tratamiento indicado para la reacción anafiláctica se recomienda el lavado gástrico. En la alergia alimentaria los antihistamínicos son útiles; los antiinflamatorios no esteroides se están ensayando, los corticosteroides orales a veces son necesarios y el cromolyn ha dado resultados inconsistentes.

José E. Sifontes, M.D., FAAP

COURSE AND OUTCOME OF CHRONIC PANCREATITIS. R.N. Ammann, A. Aboobiantz, F. Largiader, and G. Schueler, Gastroenterology 1984; 86:820-8.

Se reportan 245 pacientes con pancreatitis crónica estudiados prospectivamente por espacio de veinte años. La etiología de pancreatitis fue: alcohol en 153, idiopática en 45, hereditaria en 3, hiperparatiroidismo en 3, trauma en 2, fenacetin en 4 y otros en 2. Murieron 86 pacientes. La pancreatitis fue la causa de muerte en 16 (19%). Las causas más comunes de muerte fueron malignidades, enfermedades cardíaca, infecciones severas y complicaciones de cirugía. Se encontró un deterioro progresivo en la función pancreática y un aumento de calcificaciones pancreáticas durante el estudio. Hubo una tendencia progresiva a aliviarse del dolor abdominal. Cerca del 90% de 86 pacientes con dolor crónico y pancreatitis por alcohol tuvieron alivio completo del dolor durante el período de observación sin requerir cirugía.

Angel Olazabal, M.D.

**RANDOMIZED CONTROLLED TRIAL OF
ADENINE ARABINOSIDE MONOPHOSPHATE
FOR CHRONIC TYPE B HEPATITIS.** Hoofnagle JH,
Hanson RG, Minuk GT, et al. *Gastroenterology*
1984; 86:150-7.

Hasta el día de hoy no hay un tratamiento satisfactorio para hepatitis crónica Tipo B. El agente antiviral adenine arabinoside 5' monophosphate (Ara-AMP) se había evaluado en estudios clínicos de pocos pacientes. Los autores reportan una evaluación prospectiva donde escogieron al azar 20 pacientes a recibir Ara-AMP por 28 días o a un grupo control. Se encontró que durante el período de tratamiento con Ara-AMP los marcadores séricos de replicación viral (la polimerasa y el DNA del virus de hepatitis B) bajaron marcadamente pero que aumentaron una vez terminada la terapia. Durante el período de seguimiento, que fue de 18 meses, dos pacientes en cada grupo mostraron mejoría clínica y serológica. Efectos secundarios ocurrieron con frecuencia en el grupo tratado con Ara-AMP. Los autores concluyeron que el tratamiento con Ara-AMP no es efectivo en eliminar el virus de hepatitis B en estos pacientes.

Angel Olazabal, M.D.

**POSTEXPOSURE PROPHYLAXIS OF
HEPATITIS B; RUBELLA PREVENTION.
ADVISORY COMMITTEE FOR IMMUNIZATION
PRACTICES.** *Morbidity and Mortality Weekly Report*
1984; 33:285-290; 301-310, 315-318.

El Comité Consultor sobre Prácticas de Inmunización (CCPI) publicó recientemente sus nuevas recomendaciones para el tratamiento de personas expuestas a hepatitis b. Estas recomendaciones alteran parcialmente las guías ya publicadas para el uso de inmunoglobulinas contra hepatitis y la vacuna contra hepatitis b.^{1, 2} Anteriormente se recomendaba el uso de inmunoglobulina específica contra hepatitis b (HBIG) como profilaxis para la enfermedad. La novedad de las nuevas recomendaciones consiste en la disminución del número de dosis de HBIG y la incorporación del uso de vacuna contra hepatitis b en el tratamiento preventivo de los siguientes grupos: recién nacidos de madres con antígeno de superficie de hepatitis b (HBsAg) en sangre, personas que reciban exposiciones percutáneas a sangre contaminada (por ejemplo, pinchazos con agujas) y contactos sexuales regulares de portadores de HBsAg. Las nuevas guías especifican claramente las dosis y los itinerarios de administración de los medicamentos, y serán de utilidad para obstetras, pediatras, cirujanos, infectólogos, oficiales de control de infecciones nosocomiales y, en realidad, todo profesional de salud.

Las nuevas recomendaciones para control de rubéola proveen información sobre la vacuna, las pruebas serológicas para diagnosticar la infección, las reacciones y las contraindicaciones de la vacuna. También describen una serie de programas para la eliminación del síndrome de rubéola congénita. Los párrafos más interesantes presentan la información referente a la vacunación de mujeres de edad reproductiva. Se debe recomendar a las vacunadas que no queden embarazadas en los tres

meses después de la vacunación, y las mujeres embarazadas no deben vacunarse. Esto es para evitar riesgos teóricamente posibles para el feto. La convicción del CCPI es (y las razones se explican en el texto) que el riesgo de defectos congénitos en el feto, por vacunar una mujer en el embarazo, es tan pequeño que es "negligible" y no debe ordinariamente ser razón para considerar interrumpir el embarazo.

1. ACIP. Immune globulins for protection against viral hepatitis. *Morbidity and Mortality Weekly Report* 1981; 30:423-428, 433-435.
2. ACIP. Inactivated hepatitis b virus vaccine. *MMWR* 1982; 31:317-322, 327-328.

José G. Rigau, M.D., FAAP

**HLA-B27 AS A DIAGNOSTIC SCREENING TOOL
IN CHRONIC LOW-BACK PAIN.** Sandstrom J,
Anderson GBJ, Lennart R. *Scand J Rehab Med*
1984; 16:27-28.

The purpose of this study is to evaluate if the HLA-B27 antigen typing is of diagnostic value as a screening test for Ankylosing Spondylitis in patients with low back pain. 45 patients, 29 male, 16 female with low back pain, under 50 years of age, no signs of root compression and no signs of ankylosing spondylitis in X-Rays were screened. Six (13.3%) were HLA-B27 positive and two of this six showed radiographic signs of ankylosing spondylitis on a follow up X-Ray one year later. As control, 500 healthy blood donors of same region were screened and 10.6% were positive for HLA-B27 antigen.

The study does not indicate any significant increase of positive test among chronic low back pain patients when compared to healthy control populations.

The authors conclude that the test may be of diagnostic value when there are other symptoms and signs present, but has a very limited clinical value as a screening test for ankylosing spondylitis in patient's with low back pain.

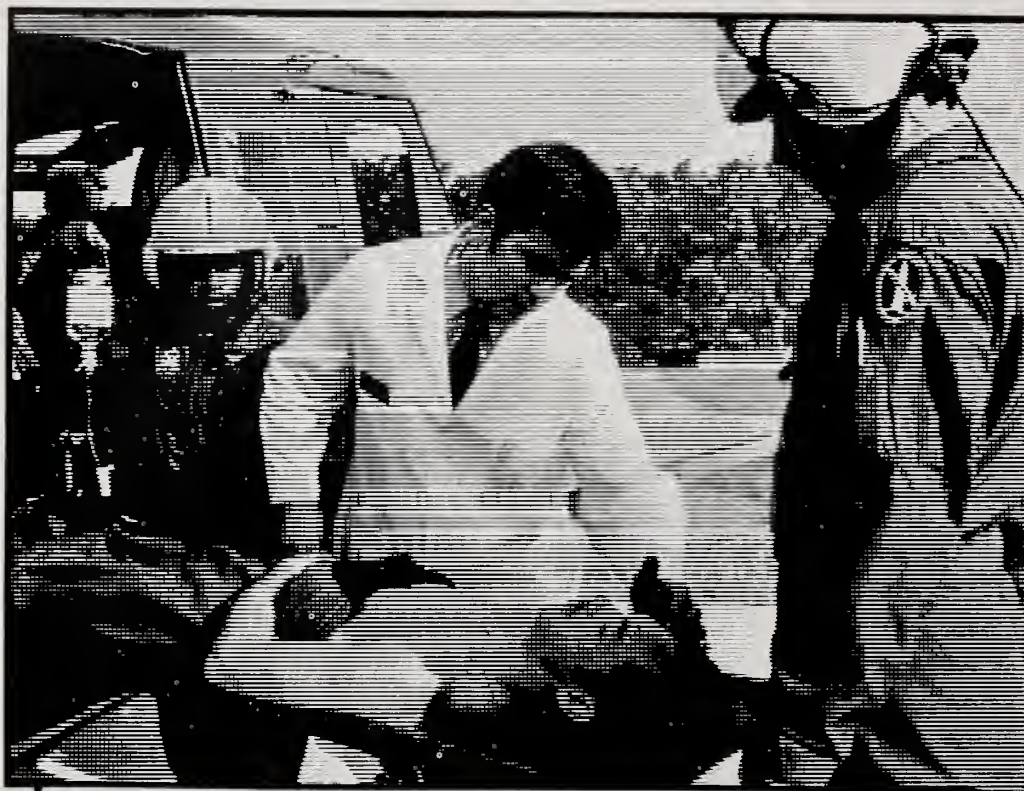
Wildo Vargas, M.D.

TIGHT-JEAN MERALGIA: HOT OR COLD.
Gilroy J *JAMA* 1984; 252:42-43

Meralgia paresthetica is an interstitial type of peripheral neuropathy caused by compression of the lateral femoral cutaneous nerve at one of its many possible sites of entrapment along its long angulated and variable courses. The two most common areas of entrapment are at the nerve's ventral emergence through or under the inguinal ligament 1 cm. medial to anterior superior iliac spine and when it pierces through the fascia lata of the anterolateral part of the thigh 10 cm. distal to the inguinal ligament. Recently, the use of liquid crystal thermograph (contact chromography) was reported as a confirmatory test for meralgia paresthetica. This condition has traditionally been termed after the specific garments associated with causing the compression of the lateral femoral cutaneous nerve. Terms associated with trusses, belts, watch pocket and back pad have been reported. Now, that jeans have become the international uniform, the clinician can expect to see more patients with tight-jeans meralgia paresthetica and if thermography is performed as a confirmatory test "hot" and "colds" lesions can be identified noninvasively.

José R. Busquets, M.D.

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American College of Cardiology

THREE-YEAR STUDY ON BALLON ANGIOPLASTY SHOWS PTCA SUCCESSFUL

Serial catheterization studies on 28 patients reveal that most patient's coronary arteries remained open when studied 3 years following balloon angioplasty, says Douglas R. Rosing, M.D., F.A.C.C., of the National Heart, Lung, and Blood Institute (NHLBI), of NIH.

Reports of functional benefits of balloon angioplasty have varied. Some cardiologists have been concerned about the frequency of reocclusion at the original site, but Dr. Rosing reported recently on the first study to follow patients for 3 years with serial catheterization. In this study, "Three-year Anatomic and Functional Follow-up After Successful Percutaneous Transluminal Coronary Angioplasty," PTCA successfully opened most patients' stenotic lesions.

During the subsequent 3 years, some patients had further spontaneous decreases in their stenosis. "I don't know how biologically significant this small anatomical improvement was," Dr. Rosing says. "What is important is that there was no anatomical deterioration after 6 months."

About 25 percent of patients do restenose at the original lesion, but this usually occurs within the first 6 months. These patients were redilated by balloon angioplasty and reentered into the study.

"No patient with a successful result at 6 months had a greater than 10 percent increase in stenosis at 3 years," Dr. Rosing says.

While the study does not reveal the cause for the restenosis, Dr. Rosing suggests it may be related to differences in balloon pressure used during the original procedure. Originally, balloon catheters were inflated to less than 6 atmospheres, but, with the development of new balloon construction, later patients received higher pressure (8-10 atmospheres) during balloon angioplasty; fewer reversions of stenotic lesions have occurred in patients done with higher inflation pressures.

More important, this successful anatomical result also is successful functionally. The patients' functional classes

improved; for the first 14 patients in the study, before PTCA one patient, asymptomatic, was Canadian Heart Classification functional class (FC) O, 8 were FC II, 16 were FC III and 3 were FC IV. Three years after, 11 patients were asymptomatic (FC O), 5 patients were FC I, 4 were FC II and 2 were FC III. Both patients in FC III had or have atherosclerotic lesions at other coronary artery sites that were not amenable to dilation.

"Many of us have believed from clinical observations and exercise ECG studies that PTCA improves patients' cardiac anatomy and function," Dr. Rosing says. "Now, this is one of the first studies to show the procedure is durable if we can get them through the first 6 months. This study gives balloon angioplasty even more credibility."

ELDERLY PATIENTS AT NO GREATER RISK IN CARDIAC SURGERY

"With today's improved techniques, the risks in cardiac surgery are no greater in the elderly than in any other patients," says John L. Ochsner, M.D., F.A.C.C., Chairman, Department of Surgery, Ochsner Clinic, and Clinical Professor of Medicine at Tulane University in New Orleans. "Just as important, yesterday's 'elderly' are not elderly today." As a larger percentage of our population nears old age, the patient once considered elderly becomes the "average" candidate for cardiac surgery.

New surgical techniques and original data correlating age and risk in cardiac surgery were presented at a symposium called "Cardiac Surgery in the Elderly."

Denton A. Cooley, M.D., F.A.C.C., surgeon-in-chief of the Texas Heart Institute, Houston, chaired the session. Dr. Ochsner was Co-Chairman.

Dr. Cooley highlighted advances in arch and thoracic aorta surgery by describing new surgical techniques to replace sections of aorta that were previously high risk procedures. "As these new techniques decrease the risks of surgery, more procedures are being carried out in the elderly," he says. "The use of induced hypothermia with complete circulatory arrest has greatly improved the outcome of cardiac surgery. New fibric grafts that are treated to prevent blood loss during the operation also have reduced surgical risks."

Dr. Cooley notes that "...in repairing or replacing aneurysms in the elderly one must be particularly supportive postoperatively because of respiratory insufficiency. Arteriosclerosis in the coronary arteries is also common in the geriatric patient. However, "the complications most feared are brain or spinal cord injuries," Dr. Cooley says. The improved technical methods discussed by Dr. Cooley at the symposium are primarily involved in protecting the central nervous system during surgery.

According to Dr. Ochsner, "Although there is always some additional risk in the elderly regardless of the type of surgery, the risk to an elderly patient undergoing cardiac surgery is almost the same as that in a 40-year-

old. We are operating on the elderly more and more frequently because they often can't be treated medically. In addition, some procedures such as balloon angioplasty are more likely to be successfully performed in the younger patient. The elderly patient is more likely to undergo surgery."

Dr. Ochsner adds that today more of a "total correction" is carried out during surgery because it is now known how to protect the heart during the procedure. "We used to do one or 2 grafts per operation. Now the average procedure is a 4-vessel bypass."

The overall risk in these procedures is an impressive "less than 1 percent." Dr. Ochsner credits much of this success to hypothermia and cardioplegia. Induced hypothermia maintains the body at 25° C. The heart itself is actually packed in ice to maintain in a temperature of less than 20° C. A cardioplegia solution containing potassium and other chemicals is administered via the aorta to put the heart to rest. The heart ceases to contract and remains in a nonmetabolic state.

Data show a high rate of surgical success in the elderly that may be attributed to these recent technical advances and has resulted in more and more cardiac surgery being performed in the elderly. Ronald M. Weintraub, M.D., F.A.C.C., associate professor of surgery at Harvard University Medical School in Boston, shared new data that show an increase in cardiac surgery in the elderly and little or no increased risk.

"Cardiac surgery has increased in the elderly simply because of demographics," Dr. Weintraub says. "In the data to be presented, 43 percent of the surgeries performed in the past year were in patients 65 years of age or older, and 27 percent were in patients 70 years or older." Dr. Weintraub anticipates a national trend of surgery being performed more often in the elderly.

In the past 9 years, Dr. Weintraub and colleagues have performed various cardiac operations on 620 patients 65 years or older. Of these, 345 were 70 years or older; 225 of these elderly patients underwent valve surgery. "In comparison to their younger counterparts, age per se was not a barrier to operation in the elderly," Dr. Weintraub says. "In particular, age is not a factor in operative mortality in aortic valve surgery. It is a factor in mitral valve surgery, however."

In this age of medical cost consciousness and the debut of DRGs, hospital length of stay and overall costs are factors when considering surgery in the elderly. Dr. Weintraub's study shows that hospital stays are longer and utilization of intensive care is somewhat extended following surgery in the elderly compared to younger patients. Overall hospital costs are consequently higher. However, Dr. Weintraub emphasized that "...long term studies show that elderly patients do very well following cardiac surgery. We see a definite improvement in their quality of life," he says. "We have been looking at a series of cardiac surgery patients with a critical eye for how the elderly we doing...and all our data point to very satisfying short—and long—term results in the elderly."

"When age is examined as an incremental factor in valvular surgery, by and large, it is not terribly significant," Dr. Weintraub concludes.

CONTROVERSIES OVER OBSTRUCTIONS IN HYPERTROPHIC CARDIOMYOPATHY

Is the ventricular septal myotomy myectomy (VSM-M) operation justified in patients with hypertrophic cardiomyopathy (HCM)? This depends on whether true obstruction exists in HCM.

This controversy, which relates to the definition of obstruction, has been continuing for almost 20 years. Traditionally, 2 types of HCM have been identified. In one type (hypertrophic obstructive cardiomyopathy, muscular or hypertrophic subaortic stenosis), an obstruction of the flow of blood from the left ventricle to the aorta is thought to exist because of the presence of large pressure gradients (pg) within the left ventricle.

However, the VSM-M operation relates to the pathophysiological importance of the pressure gradient in HCM as to whether there is true obstruction.

"It would seem the accepted perception that pg's in HCM mean obstruction is valid. Therefore, recommending the operation to severely symptomatic patients with this disease is still justified," says Barry J. Maron, M.D., F.A.C.C., chief of echocardiographic laboratory—cardiology branch at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, MD.

"This is based on the observation that the operation will abolish or significantly reduce the pg and that the overwhelming majority of these patients report or describe lasting symptomatic benefits after the operation," Dr. Maron says.

Dr. Maron's views are shared by E. Douglas Wigle, M.D., F.A.C.C., professor and chief of cardiology, Toronto General Hospital at the University of Toronto. Both Dr. Maron and Dr. Wigle have studied severe cases of the abnormality.

According to Dr. Maron, "patients with obstructive forms of HCM have unique dynamics of left ventricular emptying. There is an early ejection of substantial portion of the stroke volume, but, also during the middle portion of systole, impedance to outflow occurs. This impedance continues through late systole and appears to be due to opposition of the mitral valve with the ventricular septum."

It is also clear that patients with HCM, but no patient gradient, differ distinctly from patients with HCM and a patient gradient with regard to patterns of flow in the aorta.

Based on similar findings, Dr. Wigle says "the fact that the left ventricle continues to empty after development of the obstruction has been demonstrated angiographically, echocardiographically, and by electromagnetic flow studies."

Dr. Wigle also concludes surgery is indicated. "Surgery basically relieves all of the patho-physiological abnormalities associated with anterior mitral leaflet-septal contact in early systole. Surgery can be carried out with low risk and dramatic clinical and hemodynamic results, and is indicated in severely symptomatic cases."

Yet, other clinical data indicate that the pg's found in

patients with HCM do not mean obstruction (as in other heart conditions such as valvular aortic stenosis), according to Joseph P. Murgo, M.D., F.A.C.C., chief of cardiology service, Brooke Army Medical Center in San Antonio, TX.

Dr. Murgo believes the appearance of a pg does not translate into—or signifies—an obstruction to outflow if obstruction is defined as meaning an impediment to ejection, i.e., there is no difficulty in the left ventricle ejecting blood. The flow is not showed by the pg.

"The pg is a result of a powerful ventricular contraction and it does not, in and of itself, constitute true obstruction or impedance to left ventricular outflow. Data from their laboratory (the measured flow from left ventricle to aorta) indicate ejection is not slowed or impeded, but that it is faster than in the normal person, whether or not pg's are present."

Furthermore, according to Dr. Murgo, patients with HCM, but not a pg, also show an identical, early and rapid ejecting left ventricle. "Therefore, how can the pg be of any particular significance if all patients with HCM (regardless of whether they have a pg) have similar left ventricular ejection dynamics?" he asks.

Dr. Murgo does not recommend the VSM-M operation to eliminate "obstruction" because he does not believe true obstruction exists in patients with HCM. If the operation is successful, he believes it might because it relieves other problems that improve heart function.

For example, "there is some evidence to suggest that the operation improves the filling and relaxing function of the heart," Dr. Murgo says.

He concludes that "currently, systematic studies of the mechanics of hypertrophic cardiomyopathy are under way in a number of institutions in this country and abroad. Such studies, especially those evaluating the effects of pharmacologic and surgical interventions on diastolic performance should lead to an improved understanding of the pathophysiology of this fascinating disease."



AMERICAN ASSOCIATION
OF BLOOD BANKS

EVIDENCE MOUNTS THAT HTLV-III AND FRENCH VIRUS ARE THE SAME

Although the final word has not been issued, belief is mounting that HTLV-III, the virus discovered by Gallo et al at the National Cancer Institute, and lymphadenopathy virus (LAV), found last year at the Institut Pasteur, Paris, are one and the same.

A report in the *Journal of the American Medical Association* (June 8, 1984), states that physical analysis of the two agents is now underway and scientists from both groups are cautiously admitting that the viruses are probably the same. Results of a comparison of the protein constituents of the new agents should be available

soon. Studies for the LAV virus are ongoing at the Centers for Disease Control's new Retrovirus Branch.

Also in *JAMA*, it was announced that Cutter Laboratories will continue using the anti-core test in the hopes of reducing chances of persons with AIDS contributing to its plasma pools and avoiding costly withdrawals of its anticoagulant products from the market. Other coagulation product manufacturers are not presently following suit. Cutter estimated that recalls have cost the company about \$5 million. It has had to recall 16 lots of coagulation fractions and withheld others before distribution because donors were later diagnosed as having AIDS. The withdrawals were not required by federal regulation. Donors who have positive reactions to the test will be excluded from donating for use in making Factor VIII and IX.

Although the cost of the anti-core test is estimated at \$2.50 to \$5.00 and eliminating plasma from positive donors is also costly, Cutter does not intend at the present time to increase costs of its products.

The test for HTLV-III, the agent suspected as causing AIDS, is likely to be performed at the time of donation rather than just before transfusion, agree both Edward Brandt, MD, assistant secretary for health, and Joseph Bove, MD, chairman of the AABB Committee on Transfusion Transmitted Diseases, in *U.S. Medicine*.

Officials at the Department of Health and Human Services indicate that the test will be 100 percent accurate in detecting AIDS victims.

"I think it's warranted to screen every donor," Bove said. "I don't think the public would stand for a unit of blood that is not screened in a setting where there is a good test. It's cost that I think anybody—whether that be a person with a medical background or an ethical background or just a man or woman off the street...will say absolutely 'we want our blood screened'. My guess is that the cost of the test will be in the reasonable range and I'm sure that anybody who has anything to say about this will be enthusiastic about getting this into routine practice."

BLOOD PRODUCTS ADVISORY COMMITTEE EXAMINES AIDS ISSUES

The Food and Drug Administration's Blood Products Advisory Committee, meeting on June 6 to address current AIDS-related issues including the newly isolated HTLV-III virus, heard members and others present voice concern over proceeding too quickly toward implementation of a test before "all the facts are in". The meeting was held without a quorum, which prohibited the issuance of recommendations.

There was general agreement among the Committee members that we are "paying the price for the press conference and the resulting unrealistically high expectations." June Osborne, MD, dean of the School of Public Health at the University of Michigan and chairman of the National Heart, Lung and Blood Institute's AIDS Working Group, expressed concern over the numerous questions that remain unanswered about the HTLV-III test. "We need to ask these questions now," said

Osborne, "not after the test has been put in place across the country. The real question that we want answered is who is a risky donor, not who has the antibody because we don't know what having the antibody really means."

While others on the Committee echoed Osborn's concern, Chairman William V. Miller, MD, reminded those present of the tremendous pressure that has been brought to bear on blood banks during the past year because of the fear of transfusion-transmitted AIDS, and asked that a scholarly approach, which might be preferable under ideal circumstances, be balanced with the pragmatism of public expectations. "The American people expect a test within six months," said Miller. Osborne stated that telling prospective donors they had "flunked" the AIDS test was likely to generate greater fear in those individuals than that associated with the risks of transfusion. She alluded to the recent decision to have the HTLV-III test kits produced under an Investigational New Drug (IND) process, which "will help to curtail the wish to stampede."

Bruce Voeller, PhD, from the National Gay Task Force, and Neil Schram, MD, of the American Association of Physicians for Human Rights, expressed concern about the potential use of the new test for discrimination against homosexual men, citing possibilities of it being used to bar individuals from obtaining health and life insurance and from obtaining or maintaining jobs in hospitals or other health related organizations. Voeller stressed the need for confidentiality, particularly when the INDs are no longer under the direction of NCI.

In spite of the excitement surrounding the isolation of the HTLV-III virus, the need for continued adherence to and perhaps modification of the existing recommendations issued in March 1983 was stressed. Looking at the transfusion-associated cases which occurred prior to the institution of these guidelines and those that occurred afterward, it appears that there are about half as many AIDS cases from donated blood or plasma after the guidelines went into effect as there were prior to that time, said Miller.

The Committee considered a letter from the American Red Cross which asked for a clarification of the recommendations on several points, including a definition of "multiple sexual partners" and "recent entrants from Haiti." Schram suggested wording proposed by the American Rights, which was adopted by the American Blood Commission Board of Directors at a recent meeting. It was suggested that since members of the voluntary blood collection organizations were on the Board of the ABC, it would probably be acceptable to these organizations as well. In the question of "recent entrants from Haiti," no firm suggestions were forthcoming, but it was pointed out that since Haiti was endemic for malaria, individuals would already be excluded from donating for three years after their arrival.

The prospect for using the New York Blood Center approach throughout the country was discussed. The New York Blood Center has incorporated a mechanism into its donation system by which a donor may designate his blood be used for research rather than transfusion if there is a question about the safety of the donation. Voeller urged that this become a recommendation of the

Committee, citing the pressures on individuals to donate in a corporate blood drive setting which may result in high risk individuals giving blood.

In a response to a communication from Alpha Therapeutics regarding the time-frame to be used in making decisions on discarding lots of plasma containing units from an AIDS donor, Miller expressed his opinion that the current guidelines which call for consideration of disposition on a case-by-case basis be continued for the time being until more is known about the applicability of HTLV-III testing to this problem.



HOSTILITY AND HEART DISEASE

Hostility may be a key aspect of the "Type A" behavior profile — the hard-driving, impatient person who is at higher risk than others of having heart attacks, said Redford B. Williams, Jr., M.D., at a recent American Heart Association meeting.

Not all Type A's get heart attacks, but in studies at Duke University Medical Center in Durham, NC, over the last seven years, Type A patients showed more severe coronary heart disease than others. And the Type A's who scored high on an experimental "hostility" scale from the standard personality assessment questionnaire, the Minnesota Multiphasic Inventory (MMPI), had a particularly high rate of heart disease reported Dr. Williams, Associate Professor of Medicine and Professor of Psychiatry.

Dr. Williams studied the records of 255 physicians who had taken the MMPI 25 years earlier, while in medical school. Those who scored low on the hostility scale had a less than three percent heart attack rate during the ensuing 25 years, compared with more than a 12 percent rate for those with higher range hostility scores—nearly a five-fold difference. Their death rates from all causes followed this same pattern, being lower among the low-hostility men.

Numerous researchers are investigating the mechanisms, by putting Type A's and the more calm Type B individuals through stressful experiments in laboratories. Type A's show larger boosts in blood pressure, and larger increases in blood levels of epinephrine and cortisol, the adrenal hormones that cause blood vessels to constrict, Dr. Williams said.

The Duke researchers found, among Type A men given simple arithmetic problems, physiologic and hormonal reactions similar to those seen in emergency and fight-or-flight situations. Excessive levels of the adrenal hormones and of testosterone, the male sex hormone, have been implicated in animal studies in the hardening and narrowing of arteries.

Further studies are necessary to determine if the higher

hormonal responses observed so far in some Type A persons are causative factors in heart disease, Dr. Williams said. If susceptible people could be identified early, then preventive measures could be taken to save their lives.



NATIONAL SOCIETY FOR MEDICAL RESEARCH

PROTEIN "CAPSULE" STOPS LIVER METASTASES

A synthetic lipid sphere containing a natural serum molecule, called C-reactive protein, may prove useful in stopping the spread of colon cancer to the liver, Cleveland researchers have suggested.

The encapsulated protein, reported Dr. Sharad D. Deodhar of the Cleveland Clinic Foundation, is engulfed by the body's scavengers, cells known as macrophages, which become activated and kill tumor cells. Work with laboratory mice in which colon cancer was induced, revealed that the protein-containing lipid spheres inhibited the ability of this cancer to metastasize, or spread, to the liver.

Recently, scientists have been studying the use of liposomes in controlling metastases in experimental animals. These synthetic lipid spheres are hollow and can be used to deliver various drugs and natural biological products directly to tumors.

NSMR MEMBERS ON "ANIMALS FOR RESEARCH"

Legislation such as that in Massachusetts which prohibits use of impounded animals for research is enacted because of what legislators *believe* is public opinion. The public has not been given an opportunity to develop an informed opinion on this issue.

Nearly everyone has had a member of his family or a close friend benefit directly from lifesaving surgery and medication that was first developed and tested on animals. If the average person realized the role that animals have performed in the development of surgical techniques and new drugs, he would be grateful and would support continued use of animals.

All families wish to protect their wanted pets but most consider unwanted animals to be public nuisances. The average family would welcome better protection of wanted pets and beneficial use of unwanted animals.

Humane societies provide a desirable social service by restoring lost pets to their owners and providing good care for unwanted animals until new homes are found for them or until the animals are euthanatized. However, humane societies actually do the public a disservice by destroying unwanted pets. Those who believe in conser-

vation of resources should be concerned about such a practice. The cost of replacing those animals to provide for the needs of research is formidable.

One possible solution would be the establishment of foundations with much the same function as humane societies with one specific exception: unwanted animals would be made available to approved research institutions rather than being euthanatized. Animals would be acquired only by donation. Donors would legally relinquish all rights to the animals and in return would be able to claim a tax deduction.

The donor would be expected to provide information regarding origin, care and medical history for each donated animal. This information would be valuable to subsequent owners who adopt the animals and to researchers who receive the unwanted ones. The animals available for research would be healthier than those currently obtained from dealers because the animals would receive good care from the time of donation and would not be transported great distances under crowded conditions.

Pet owners would benefit because their pets would no longer be prey for some dealers who have long been notorious for their unscrupulous methods of acquiring animals. Research institutions would legally own donated animals and could utilize local animals without fear of confrontation by irate pet owners.

Companion animals themselves could well derive the greatest benefits because much of the research conducted on them would be applicable to them. Experienced breeders of animals realize that birth defects and genetic diseases are a universal problem and are generally willing to donate defective animals with the hope that effective therapy and counseling will become available.

A wealth of animal models could be derived from this source. At present most potential models are lost because there are no facilities or funds available to maintain the animals when they are offered.

The animal facility maintained by the foundation could have all the appeal of the humane society and more. Because the animals would be maintained primarily for research, it would be appropriate to encourage schools and other educational organizations to use the animals in their projects. Participants would be given instruction on the proper care of animals. Volunteer help from educational organizations and from the general public should be encouraged.

Above all, it is the general public that must be convinced of the value of using animals in research. Currently taking unwanted pets to the humane society rather than dumping them in a rural area is "the thing to do." The humane societies have made progress in the right direction. In a technological age, it seems reasonable to expect that donating animals for research should become socially acceptable. Establishing foundations to promote animals for research and giving the public an opportunity to take an active role in their development may be the way to turn the tide.



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This program has been developed so that the practicing clinician may evaluate the usefulness, indications and limitations of the growing fields of two-dimensional echocardiography and cardiac nuclear imaging. A careful appraisal of the comparisons and contrasts of these techniques are discussed in relationship to specific clinical problems. Cost effectiveness in particular clinical settings will be highlighted. The relationship of these noninvasive techniques to invasive, diagnostic and therapeutic modalities in ischemic heart disease and valvular heart disease will also be discussed. Advances in echocardiography and nuclear imaging techniques will be presented as well as the exciting emerging techniques of digital subtraction angiography and nuclear magnetic resonance. Maximum audience participation and faculty interaction will be fostered by several panel discussions after topical presentations. We plan to provide the participants with an understanding of noninvasive technology so that the technical aspects of the diagnostic equipment can be better understood. A program syllabus is also planned to help guide the participants through the program.

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PERTUSSIS VACCINE BENEFITS OUTWEIGH RISKS: CDC STUDY

Researchers at the Centers for Disease Control in Atlanta have completed a cost-benefit study of pertussis vaccine and conclude that continued use of the vaccine, with precautions, is the best course of action.

Alan R. Hinman, MD, and Jeffrey P. Koplan, MD, writing in the June 15 issue of JAMA, base their conclusions on a hypothetical cohort of one million children followed from birth to 6 years with and without a pertussis vaccination program. They demonstrate that a vaccination program reaching 90 percent of the children would reduce disease incidence and disease-related costs by 90 percent. The ratio of overall costs without a program to costs with a program is 5.7 to 1, and the benefit-cost ratio is 11.1 to 1, they add.

Since 1974, there has been intense debate concerning the risk of serious reactions to the pertussis vaccine, which has led to a decline in its use, the researchers point out. There have been cases of severe acute encephalopathy with permanent residual brain damage. The researchers note that some media presentations on the dangers of the vaccine have minimized its benefits. "The current low levels of reported disease make the adverse events associated with vaccine seem relatively prominent," they say.

Pertussis was once a major cause of childhood morbidity and mortality in the United States, with 265,269 cases and 7,518 deaths reported in 1934. The introduction of pertussis vaccines in the 1940s greatly accelerated the decline of the disease. In recent years, only 1,000 to 3,000 cases and five to 20 deaths are reported annually.

The researchers suggest that a safer vaccine may become available in the next two to five years. "We all look forward to the day when pertussis vaccines are developed that are equally effective as the current ones and less associated with adverse events," they say. But for now, based on the results of this and other studies, they conclude that the benefits of the current vaccination program far outweigh the risks and costs involved.

ORAL CHARCOAL EFFECTIVE FOR DRUG OVERDOSE

According to two reports in the June issue of JAMA, oral activated charcoal is an effective treatment for drug overdose.

The first report, by Peter Gal, PharmD, and colleagues at the University of North Carolina at Chapel Hill, describes the use of oral activated charcoal to treat a 23-year-old woman who had ingested 20 tablets each of terbutaline sulfate and theophylline (Theo-Dur). The serum theophylline half-life fell significantly after administration of oral activated charcoal, 50 g, every six hours.

The researchers conclude, "While hemoperfusion using charcoal or resin appears to be the most efficient method for removing theophylline, oral activated charcoal is less expensive, more widely accessible, and probably safer." They add that not only has it been reported to absorb drugs, but it also appears to promote drug elimination, thereby shortening the duration of toxic symptoms.

The second report describes a study by Susan M. Pond, MBBS, and colleagues, of the University of California, San Francisco, on the effectiveness of repeated oral doses of activated charcoal in treating phenobarbital overdose. They found that while the charcoal therapy significantly increased elimination of phenobarbital, it had no clear effect on the patients' clinical course.

All ten patients in this study were comatose and all received an initial dose of activated charcoal and cathartic. Five were given repeated doses of 17 g of activated charcoal in 70 mL of 70 percent sorbitol every four hours. All patients in both groups received supportive care in the intensive care unit, including mechanical ventilation and administration of fluids.

The length of time that patients in the two groups required mechanical ventilation did not differ significantly, and the single-dose group met criteria for extubation with higher serum phenobarbital concentrations than the repeated-dose group, the researchers say. Based on the results of this small randomized trial, repeated doses of oral activated charcoal significantly reduce phenobarbital half-life but do not significantly hasten the patient's recovery from an overdose of phenobarbital.

UNIQUE FINDING RELATING TO HYPERTENSION REPORTED

A unique finding by Charles B. Anderson, MD, and colleagues from the Washington University School of Medicine in St. Louis may lead to a rethinking of the physiology of hypertension caused by occlusion of kidney arteries. Writing in the June 15 issue of JAMA, the researchers report they were able to study prostaglandin production in a patient's kidney that had three

distinct zones of blood flow. They found variations in prostaglandin production from 2.2 to 11.3 in the most severely ischemic tissue. Commenting on the finding, G.A. Fitzgerald, MD, and D.J. Fitzgerald, MB, of Vanderbilt University, say, "The article by Anderson et al. provides information on the intrarenal production of thromboxane A₂ in human renovascular hypertension. Although we do not yet know the biologic importance of their observations, the hypotensive effect of a thromboxane synthetase inhibitor in a canine model of renovascular hypertension is indeed provocative."

PHYSICIANS MAY HELP PREVENT CHILD ABUSE

The June 22 Landmark Article in the *Journal of the American Medical Association* discusses the physician's role in intervening when confronted with apparent cases of child abuse. The article, "The Battered-Child Syndrome," written by C. Henry Kempe, MD, was first published in the July 7, 1962, JAMA.

Kempe noted that physical abuse by parents or guardians is a significant cause of childhood disability and death, and that most cases occur in children aged three years or younger. He encouraged physicians to take an active role in investigating and trying to resolve problems of domestic abuse. Kempe added, "A physician needs to have a high level of suspicion in instances... where the degree and type of injury is at variance with the history given regarding its occurrence or in any child who dies suddenly."

Commenting on the article in a "Landmark Perspective," Marilyn Heins, MD, of the University of Arizona, Tucson, says that current reporting statutes in all 50 states are a direct result of Kempe's work. "Violence against infants and children is at least as old as recorded history," Heins points out, but now more is known about the factors leading to abuse. Heins notes that medical schools and the AMA are providing leadership in helping physicians to recognize, treat and prevent cases of child abuse.

NEW ACNE DRUG CAN CAUSE BIRTH DEFECTS

A warning that a drug used for severe acne can cause birth defects in infants appears in the June 22 issue of JAMA.

A researcher from the University of Miami School of Medicine reports on two infants born with a series of anomalies, including hydrocephalus, malformed ears, small mouth and cleft palate. Both mothers had taken isotretinoin (Accutane) in the first trimester of pregnancy, says Paul J. Benke, MD, PhD. Neither child survived.

"Accumulating experience suggests that isotretinoin is one of the most severe teratogens seen to date in man," Benke says. "Large amounts of isotretinoin ingestion by the mother are not required for the appearance of dramatic and devastating features in the newborn."

Isotretinoin is a retinoic (vitamin A) acid that inhibits the production of sebaceous gland lipid, and it is very effective in severe nodular and cystic acne of the type that causes marked scarring. Among other actions, the drug reduces the size of the sebaceous gland. It has been marketed in the United States since September 1982.

"Most likely, isotretinoin will be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including systemic antibiotics, because of its potential for severe side effects," according to the current edition of the *AMA Drug Evaluations*.

Researcher Benke observes that the teratogenicity of isotretinoin was well known as a result of animal studies and that some reports of spontaneous abortions and birth anomalies have been reported. As a result, the drug has been listed as a severe hazard during pregnancy by the Food and Drug Administration.

"The effects of isotretinoin teratogenicity have not been presented in detail," he says. "This report describes two infants with central nervous system, ear, and facial malformations, born after maternal ingestion of isotretinoin during early pregnancy. These features were distinct and constitute a recognizable syndrome in infants so exposed."

BB GUNS CAUSE SEVERE INJURIES

More than 50,000 injuries resulted from misuse of BB guns and air rifles during 1980 and 1981, according to a study in the June *American Journal of Diseases of Children*. Katherine K. Christoffel, MD, MPH, and colleagues from Chicago's Northwestern University Medical School say that 80 percent of the injuries are sustained by young males between the ages of 5 and 24 (54 percent between 5 and 14). "Current government regulation of nonpowder firearms is not as strict as the severity and prevalence of injuries warrant," the researchers say. Injuries include retinal detachment, intra-abdominal hemorrhage, and lead poisoning.

TARDIVE DYSKINESIA DIFFICULT TO REVERSE

A study of 33 psychiatric patients with tardive dyskinesia (involuntary body movements induced by long-term use of antipsychotic drugs) showed that only one demonstrated complete reversal following discontinuation of antipsychotic therapy during a one-year period. "Since tardive dyskinesia was fully reversed in only one patient in our study, caution should be exercised in using neuroleptics in the first place, especially for the nonschizophrenic patients," say William M. Glazer, MD, of Yale University School of Medicine, and colleagues writing in the June *Archives of General Psychiatry*.



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Medicolegal Decisions



PATIENT SUES FOR LATE DIAGNOSIS OF ILLNESS

A patient could not recover on a jury verdict against physicians, a lab technician, and a hospital because he agreed to credit them with the amount of a settlement he received from some of them, a New Mexico appellate court ruled.

The patient was born on February 3, 1976. A pediatrician began caring for the patient five days after he was discharged. His mother took him back to the hospital for a PKU test on February 9, 1976, and again on February 11, 1976. Because of continued problems with the baby's crying and feeding, his parents took him to another hospital, where brain damage caused by bilirubin encephalopathy was diagnosed.

Prior to trial, the patient settled with the pediatrician, the hospital, and lab technician. After a trial, the jury returned a verdict for the patient in the amount of \$510,000. The amount of settlement was much larger than the verdict, and the trial court ruled that the patient was not entitled to additional recovery.

On appeal, the patient argued that he was entitled to recover 15 per cent of the \$500,000 from one of the physicians who did not settle because the jury found him 15 per cent negligent. The court noted that the patient had agreed to credit the amount of the settlement against any recovery from the non-settling physicians. The patient could not recover any additional amount from the physician.

The court rejected the parents' claim for mental anguish, since they were bystanders and did not observe any sudden trauma involving their son. New Mexico also did not recognize an action by parents for loss of companionship of a child.

The court affirmed the trial court's decision but remanded for the trial court to assess costs.—*Wilson v. Galt*, 668 P.2d 1104 (N.M.Ct. of App., June 21, 1983; cert. quashed, Aug. 19, 1983)

PSYCHIATRISTS MUST PRODUCE RECORDS IN INVESTIGATION

Two psychiatrists had to produce patient records or be found in contempt, a federal appellate court for Michigan ruled.

A federal grand jury issued subpoenas to the two psychiatrists during an investigation of alleged fraudulent billings submitted to Michigan Blue Cross/Blue Shield. The subpoenas sought only patient identities, the dates on which they were treated, and the length of their treatment on each date. The psychiatrists contended that the information was protected from disclosure by a psychotherapist-patient privilege. A trial court found the physicians in contempt of court, and they appealed.

Affirming the decision, the appellate court said that the identity of the patients and dates and times of treatment did not fall within the scope of the psychotherapist-patient privilege. Disclosure of that information did not infringe on the privacy rights of patients because the grand jury already knew the patient's names from the insurance forms in its possession. The information was also protected by the veil of secrecy attending grand jury proceedings.

The psychiatrists could not claim the Fifth Amendment to bar production of the records because the records were records of a professional corporation rather than private ones. The right to be free from self-incrimination did not apply to corporations, the court concluded.—*In re Zuñiga*, 714 F.2d 632 (C.A. 6, Mich., Aug. 3, 1983)

MD SUES PSYCHIATRIST FOR DISCLOSING CONFIDENCES

A psychiatrist was entitled to summary judgment where his affidavit that a patient had authorized him to disclose a diagnosis to an insurer was not opposed by a sufficient factual issue, a New York appellate court ruled.

The patient was a licensed physician enrolled as a student in a postgraduate psychoanalytic training school. A requirement of the course of study was that he undergo analysis with a psychiatrist appointed by the school.

The patient unilaterally terminated his analysis with the psychiatrist and was subsequently denied certification by the school. In a suit against the psychiatrist, the patient alleged that he conducted the analysis negligently because he violated a confidentiality agreement made before the analysis started. The psychiatrist's motion for summary judgment was denied.

On appeal, the court said that the only relevant evidence was found in the psychiatrist's affidavit and excerpts of a pretrial examination of the patient. In the affidavit, the psychiatrist stated that the patient authorized him to disclose the diagnosis of his mental condition to his medical insurer so that he could be reimbursed for fees paid to the psychiatrist. He said that he had informed the patient that he would have to notify the school's student committee that he wished to discontinue analysis but did not disclose anything beyond this to the committee. In his pretrial examination, the patient

confirmed the psychiatrist's statements.

The appellate court granting the psychiatrist's motion for summary judgment found that the patient's opposing papers were insufficient to create a factual issue.—*Dove v. Young*, 463 N.Y.S.2d 460 (N.Y. Sup. Ct., App. Div., June 9, 1983)

MD HELD IN CONTEMPT FOR FAILURE TO PRODUCE RECORDS

A psychiatrist was properly held in contempt of court for failure to comply with a subpoena to produce medical and prescription records, a federal appellate court in New York ruled.

In 1981, the DEA began an investigation of a medical clinic and several persons associated with it. The government furnished evidence to a grand jury that the clinic was engaged in large-scale illegal distribution of Quaalude tablets to both consumers and street dealers. The government's evidence showed that the physician was paid \$3,000 for each day he worked at the clinic. He saw 590 patient (an average of more than 70 per day) while associated with the clinic. Over 90 per cent of the patients received prescriptions for 30 to 60 Quaalude tablets. Each patient was given a perfunctory physical exam and a brief interview with a physician. All that was required of a patient to obtain a prescription was a claimed sleeping difficulty, denial of drug abuse, and a cash payment of \$150 to \$200.

The grand jury issued a subpoena to the physician directing him to produce his patient files, financial records, and Schedule II prescription forms. A trial court ordered him to comply with the subpoena and he declined. The court held him in contempt, and he appealed.

Affirming the decision, the court said that the psychiatrist could not rely on his Fifth Amendment privilege not to comply with the subpoena. He must produce his W-2 forms, and prescription and patient records, the court said. Although his compliance with the subpoena might be self-incriminating, the subpoenaed records fell under the required records exception to the Fifth Amendment. He could not argue that the records were self-incriminating since they were required to be kept by state and federal laws. The psychiatrist-patient privilege did not prohibit him from disclosing the records, since no real psychotherapist-patient privilege existed, the court said.—*Doe v. U.S.*, 711 F.2d 1187 (C.A.2, N.Y., June 29, 1983)

HOSPITAL NOT NEGLIGENT IN X-RAY TEST ON PATIENT

A hospital was not negligent in performing a diagnostic X-ray procedure on a patient, an Illinois appellate court ruled.

The patient entered the hospital for correction of a bladder problem. Early in the morning of May 22, 1978, X-rays of her kidneys were made. As part of that procedure, a dye was injected intravenously to give a clearer image of the kidneys on the X-ray films. The X-ray technologist explained the test procedure to her and

asked about her allergies. There was no result from the sensitivity test and the entire 50 mls. was injected.

About three hours later she was returned to the X-ray department for a cystogram test. She was seated in a wheelchair in a corridor in the X-ray department. The technologist noticed that she was having a seizure. Her head and neck went rigid. He and the physician put her on a stretcher and took her to the emergency room. X-rays disclosed a compression fracture of the 11th thoracic vertebra, possibly caused during the seizure. A trial court directed a verdict in favor of the hospital, and the patient appealed.

Affirming the decision, the court said that the patient had not made out a case for the application of *res ipsa loquitur*. The evidence was in controversy on whether the seizure some three hours after the injection was an occurrence that did not ordinarily happen in the absence of negligence. There was also insufficient evidence that the cause of the patient's seizure was in the exclusive control of hospital.—*McMillen v. Carlinville Area Hospital*, 450 N.E.2d 5 (Ill.App.Ct., May 25, 1983; rehearing denied, June 15, 1983)

NO NEGLIGENCE IN CARE OF CHRONIC IRITIS

A physician was not negligent in treating a patient for chronic iritis, the Washington Supreme Court ruled.

The physician prescribed topical corticosteroids and systemic corticosteroids. He also prescribed topical atropine for her iritis in November 1976. In January 1977, she began to see flashing lights, wavy lines, and spider webs. She went to one of the physician's associates, and he administered an injection. Her visual problems continued and in February she began to feel pressure in her right eye. The physician increased her medication, but her pain worsened.

On March 18, 1977, she made an emergency visit to another associate. He tested her intraocular pressure and found it to be extremely high. He diagnosed an acute glaucoma attack, and she was rushed to a hospital for emergency surgery. Since then, she was hospitalized several times with eye problems and suffered a severe deterioration in her vision and attendant psychological problems.

She filed suit against her physician and a pharmacist. She claimed that the pharmacist mistakenly dispensed Isopto-Carpine instead of atropine eye drops and that the drops should not be used by patients with iritis. She also contended that the physician was negligent in not detecting her glaucoma. A jury returned a verdict against the patient and she appealed.

Affirming the decision, the Supreme Court said that the standard of care applicable to health care providers was a standard of care of reasonable prudence, not an "average practitioner" standard. Nonphysicians, if otherwise qualified, may give expert testimony in a medical malpractice case, the court said. The trial court did not err in limiting the expert testimony of a nonphysician because his testimony was not limited solely because he was not a physician, the court said.—*Harris v. Robert C. Groth, M.D., Inc.*, P.S., 663 P.2d 113 (Wash. Sup. Ct., April 18, 1983)



La 82 ava. Convención Anual de la Asociación Médica de Puerto Rico se celebrará del **8 al 12 de noviembre** en el Centro de Convenciones del Condado.

El tema seleccionado para este año es el de **Servicios de Salud Ambulatorios**, la nueva tendencia del campo de la salud que tantas inquietudes ha despertado.

El programa de actividades incluye más de treinta Seminarios de Educación Continua en los cuales se destaca renombradas figuras científicas de relevancia internacional. Se ofrecerán, además, variadas actividades sociales como atracciones opcionales libres a selección de acuerdo a preferencias individuales.

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Están incluidas en el programa varias secciones de "Temas Libres" para que todos aquellos médicos que deseen exponer casos interesantes, tengan la oportunidad de hacerlo. Se celebrarán "Secciones de Afiches" o "Poster Sessions" diariamente en los cuales los médicos que así lo deseen tengan la opción de exponer sus casos singulares o de interés particular por escrito o con elementos gráficos y discutirlos personalmente con los médicos asistentes.

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, light-headedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. **Adults:** 30 mg usual dosage; 15 mg may suffice in some patients. **Elderly or debilitated patients:** 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



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VOL. 76 / NUM. 10

OCTUBRE 1984



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ASOCIACION MEDICA DE PUERTO RICO

BOLETIN



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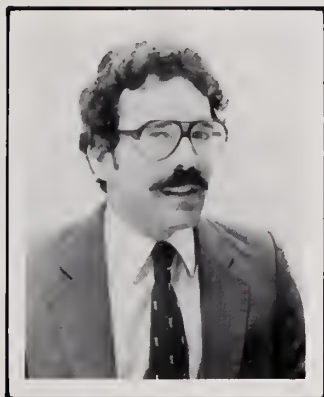
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Columna del Editor



Pensando en la proximidad entre las elecciones generales y la circulación de este número, la Junta Editora solicitó por escrito de cada uno de los candidatos a gobernador nos hiciesen saber (con intenciones de publicar) cuales en su opinión eran los dos problemas principales de salud del país y que harían ellos por resolverlos. La carta se envió certificada con acuso de recibo el día 2 de julio pasado. En ella se les explicaban detalles de nuestra revista, y que era el órgano oficial de esta institución. Incluso se les sugirió un esquema de tiempo donde se proveía para la revisión y corrección de los trabajos antes de publicarse. Al día que escribimos, lo único que tenemos relacionado con nuestra petición son las tarjetas de correo donde se indica que recibieron nuestra carta. Ninguno envió el manuscrito ni se excusó por no haberlo hecho. Interpreto tal acción como una

descortesía crasa hacia la mayor agrupación médica de la isla y un unánime desinterés en dar a conocer por escrito sus planes para resolver estos problemas. Quizás esta sea la expresión más espontánea y sincera del desconocimiento de los agobiantes problemas de salud de Puerto Rico por parte de los políticos de turno. Quizás su respuesta es un indicio de lo que piensan hacer por resolverlos: nada.

Sin embargo por desagradable y frustrante que haya sido esta experiencia, la misma tiene dos aspectos "positivos": el primero es que por primera vez en la historia política moderna del país, los candidatos han estado unánimemente de acuerdo en algo en un año electoral. Una lástima que esta unanimidad haya sido en ignorar la petición de publicación de sus puntos de vista sobre algo tan importante para nuestra clase y nuestro pueblo. El segundo aspecto positivo es uno mas bien personal, pues al no enviar los manuscritos que les solicitamos, este Editor no tuvo necesidad de posponer la publicación de ninguno de los excelentes artículos que aparecen en este número para darle cabida a los de los candidatos. De esta manera nuestros queridos lectores pueden disfrutar de un Boletín de gran diversidad temática, valor práctico y provecho académico. La actitud de los políticos da lugar a pensar que de haber sucedido lo contrario, se hubiesen perdido todas esas características tan preciadas para una revista seria y de reconocida calidad científica como la nuestra.

Rafael Villavicencio, MD, FACC
Presidente Junta Editora
Boletín Asociación Médica de Puerto Rico

ASOCIACIÓN MÉDICA DE PUERTO RICO

BOLETÍN



VOL. 76/NUM. 10 OCTUBRE 1984

NUESTRA PORTADA:

"Los Santos" -óleo en lienzo sobre tema de naturaleza muerta representa un rincón del taller del artista. La habilidad de sacar una obra de arte sobre temas tan sencillos es una de las características del maestro Rafael Tufiño. Evidencia también el cuadro el magistral manejo de los colores incluyendo su particular uso de los azules y amarillos. Hecho en 1981 este cuadro marcó el comienzo de la presente etapa de producción artística luego de graves problemas oculares que amenazaron terminar con su obra que ya al presente lo cualifica como uno de los grandes maestros de la pintura puertorriqueña. Además de ser valioso ejemplo de pintura, el cuadro también ilustra otro renglón del quehacer artístico puertorriqueño: el arte de la santería.

Esta obra estuvo expuesta en el Taller-Galería André en Hato Rey y actualmente pertenece a la colección privada del Dr. Angel Luis Rodríguez-Rosado por cuya gentileza la hemos podido reproducir en nuestra portada.



PROGRAMA

**Programa Preliminar 82 da. Convención Anual
de la Asociación Médica de Puerto Rico
8-12 de noviembre del 1984
Centro de Convenciones del Condado**

Tema: Servicios de Salud Ambulatorios

Jueves, 8 de noviembre:

- P.M. Torneo de Golf - Director, Dr. Ricardo Méndez Bryan
2:00 P.M. Inscripciones - Centro de Convenciones
7:30 P.M. Recepción Inaugural - Centro de Convenciones

Viernes, 9 de noviembre:

- 7:30 A.M. Inscripciones - Centro de Convenciones
9:00 A.M. Seminarios de Educación Continua:
Oftalmología — Director: Dr. Jorge J. Ramírez.
Hipertensión — Director: Dr. Manuel Martínez Maldonado.
Gastroenterología — Director: Dr. Adán Nigaglioni,
Co-Moderador: Dr. Luis González Colón.
Rehabilitación — Director: Dr. Carlos Villafañá.
12:00 P.M. "Poster Session"
2:00 P.M. Seminarios de Educación Continua:
Resucitación Cardiopulmonar —
Requisito para Licencia, matrícula limitada.
Auspiciado por la Asociación del Corazón.
Director: Dr. Miguel Colón Morales
Reumatología a Nivel Ambulatorio —
Director: Dr. Alejandro E. Franco.
Análisis Transaccional en el manejo de Depresión y
Ansiedad - Esquema para el Médico Primario -
Director: Dr. Héctor A. Feliciano.
Póngase al Día en Dermatología —
Director: Dr. Jorge L. Sánchez.
Temas Libres — Hospital de Veteranos
Curso de Apreciación de Vinos para los Cónyuges —
Auspiciado por la Universidad del Sagrado Corazón y el
Segundo Festival Internacional del Vino.
Conferenciantes: -Dr. Pedro J. Borrás, Dr. Francisco Sifre,
Sr. Domingo Pagán, Lcdo. Francisco Acevedo.
5:00 P.M. Torneo de Dominó en el Área de Exhibiciones
Coctel ("Happy Hour") en el área de exhibiciones.
7:00 P.M. Cena — Numerosos restaurantes del área disponibles.

Sábado, 10 de noviembre

- 9:00 A.M. Reunión de la Cámara de Delegados
Seminarios de Educación Continua:
Fundamentos Básicos de Administración en Oficina
Médica — Directora: Sra. Ada Pérez.
Patofisiología, Epidemiología y Diagnóstico de las Infecciones
del Tracto Urinario — Director: Dr. Carlos H. Ramírez Ronda.

Diagnóstico y Tratamiento de Tuberculosis —
Director: Dr. Ramón Figueroa Lebrón.

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Director: T.G. Hiebert, PhD, M.D.

Hematología — Director: Dr. Enrique Vélez García

12:00 M. "Poster Session" en el Área de Exhibiciones.

2:00 P.M. Seminarios de Educación Continua:

Conceptos Básicos de Computadoras — Director:
Sr. Jorge Calaf

Oncología Médica — Director: Dr. Enrique Vélez García

Enfermedades Pulmonares — Director:
Dr. Ramón Figueroa Lebrón

"Medical Evaluation for Disability Claims" — American
Evaluation Research Institute — Director: T.G. Hiebert,
Phd, M.D.

Temas Libres

5:00 P.M. Torneo de Dominó en el Área de Exhibiciones
Coctel ("Happy Hour") en el Área de Exhibiciones

6:00 P.M. Coctel de Ex Presidentes A.M.P.R.
Asociación Médica de Puerto Rico.

7:00 P.M. Fiesta Tropical — Centro de Convenciones

Domingo, 11 de noviembre:

- 9:00 A.M. Seminarios de Educación Continua:
Curso de Relaciones Públicas - Director: Sr. Sixto Toro
Resucitación Cardiopulmonar (2) — Director:
Dr. Miguel Colón Morales
"Medical Evaluation for Disability Claims" — Director:
T.G. Hiebert, PhD, M.D.
Endocrinología — Director: Dr. Julián Vázquez Plard.
Tomografía Computarizada (CT) y su Impacto en la
Práctica de la Medicina Hoy — Director: Dr. Heriberto
Pagán-Sáez.
12:00 M. "Poster Session"
2:00 P.M. Seminarios de Educación Continua:
Ginecología — Director: Dr. Edward O'Neill
"Medical Evaluation for Disability Claims" — American
Evaluation Research Institute.
Director: T.G. Hiebert, PhD, M.D.
Sanografía — Director: Dr. Roberto J. Sein.
Medical Malpractice Seminar
Temas Libres - Hospital Universitario
5:00 P.M. Torneo de Dominó en el Área de Exhibiciones
Coctel ("Happy Hour") en el Área de Exhibiciones

Lunes, 12 de noviembre:

- 9:00 A.M. Seminarios de Educación Continua:
Importancia de la Sexualidad Humana en el Campo de
la Medicina — Director: Dr. Alejandro López Deynes.
Hiperalimentación — Directora: Lcda. Sania Pagán
Colón.
Cardiología - Director: Dr. Agustín Muñoz.
Pediatría — Director: Dr. William Miranda.
Control de Costos — Director: Dr. Ovidio Rodríguez
12:00 M. Conferencia Magistral
"Dr. Ramón M. Suárez" Dr. Antonio Vayés de Luna.
1:30 P.M. Banquete de Toma de Posesión — Centro de
Convenciones.

EDITORIAL



The University of Puerto Rico Hospital

The University Hospital has served for many years as the main teaching institution of the University of Puerto Rico School of Medicine. It has also provided an excellent patient population for the training of Interns and Residents in the various medical disciplines. In turn, this population has received and continues to receive an outstanding medical service. These physicians are now working as practitioners, teachers, researchers, administrators and even politicians. The scarcity of physicians in the latter group might be one of our problems.

Curiously enough, the University Hospital, although located in Río Piedras in the premises of the Puerto Rico Medical Center, by choice of the planners of the Medical School and Medical Center, has no constituency. Although it serves the entire Island and is the end referral stage for all tertiary and complicated cases, there is no commitment to help or defend this venerable institution. The University Hospital has no legislators interested in its well being or future developments, in contrast to some large and small communities which have requested and obtained the construction of area hospitals, even though, most of them are underutilized, understaffed and without adequate facilities to provide medical care of excellence. Although the University Hospital is located in Río Piedras, the population of the entire Metropolitan Area is treated at, and therefore is only interested in, the welfare of the San Juan City Hospital.

The situation is further complicated by virtue of the University Hospital being a hybrid within the Puerto Rico Medical Center Complex, with no one dedicated to the best interest of the former. There is an evident conflict of interest in the administration of the Hospital. The main problem seems to be the intricacies of the Puerto Rico Medical Center—the actual struggle of the institutions to survive while purchasing expensive services from the Medical Center. The Secretary of Health, whoever he or she might be, would want to control the University Hospital as a referral center, since aside from the Governor, he is the ultimate governmental officer responsible for the health of our people.

On the other hand, the medical accrediting agencies emphasize on the adequate control of the hospitals utilized for the teaching of medical students. To comply with this requirement, and simultaneously to overcome the lack of constituency and the conflict of interest, the following alternatives are submitted for consideration:

1. Transfer the University Hospital to the University of Puerto Rico. This will provide the Medical Sciences Campus an absolute control of its teaching hospital

which will markedly improve the administrative, service and teaching components. The Medical Sciences Campus Officials should confront no serious difficulties in achieving this goal considering that our School is the state medical school.

2. Create the position of Chief Executive Officer at the University Hospital with a Board of Directors with representation from the School of Medicine, but separate from the Puerto Rico Medical Center and its Board reporting and responding directly to the Secretary of Health.

3. Build a truly University Hospital, by the University of Puerto Rico, totally independent from the Medical Center.

If the first alternative is favored, the Secretary of Health must ensure that the indigent population be given preferential admission and treatment privileges. Similarly the continuing acceptance of all tertiary and supratertiary cases from all over the Island must be guaranteed. I am convinced no one will object the above since this has been the accepted practice.

In regard to the third alternative it is understood that this could be the most difficult to attain.

No matter which alternative is finally selected or even if no decision is made in this respect, both the Pediatric University Hospital and the adult University Hospital should strive to become as independent from the Medical Center as possible. The University Hospital, more so than the Pediatric Hospital, is a captive institution. Both should be permitted to construct their own operating room facilities as well as X-Ray, laboratory and pathology services. This will permit the realization of the elusive geographical full time, improve the case mix in favor of the institution, as well as provide ambulatory surgery to a large segment of the population.

In essence, this is not a medical but a political problem. The politicians should heed to the claims of the Medical Science Campus to administer the University Hospital based on what is best in the interest of patient care and medical education.

Enrique Vázquez Quintana, M.D.

Enrique Vázquez Quintana, M.D.
Director Department of Surgery
Medical Sciences Campus
Río Piedras, Puerto Rico



HOSPITAL PEDIATRICO UNIVERSITARIO DR. ANTONIO ORTIZ RECINTO DE CIENCIAS MEDICAS UNIVERSIDAD DE PUERTO RICO

CELEBRACION SEGUNDO ANIVERSARIO

Octubre 21 - 23, 1984

SESION CIENTIFICA

Domingo, 21 de octubre - 8:30 A.M. - 1:30 P.M.

- | | |
|--------------------|--|
| 9:00 - 9:10 A.M. | Bienvenida e Introducción Sobre El Hospital Pediátrico Universitario |
| 9:10 - 9:30 A.M. | Actualización en Asma Bronquial
Pedro Mayol, MD |
| 9:30 - 9:40 A.M. | Preguntas y Respuestas |
| 9:40 - 10:00 A.M. | Otorinolaringología Pediátrica
Nelson Fernández Blasini, MD |
| 10:00 - 10:10 A.M. | Preguntas y Respuestas |
| 10:10 - 10:30 A.M. | Sinusitis Aguda en Niños
Ramón Montes, MD |
| 10:30 - 10:40 A.M. | Preguntas y Respuestas |
| 10:40 - 11:00 A.M. | Receso |
| 11:10 - 11:30 A.M. | Educación Médica en Puerto Rico con Enfoque en la Pediatría
Pedro J. Santiago Borrero, MD |
| 11:30 - 11:40 A.M. | Preguntas y Respuestas |
| 11:40 - 12:00 A.M. | Cuidado Intensivo Neonatal en el Hospital Pediátrico Universitario
Rafael Zapata, MD |

12:00 - 12:10 A.M.

Preguntas y Respuestas

12:10 - 12:30 A.M.

Variaciones en el Ritmo Cardíaco en el Hospital de Distrito de Ponce
Francisco Torres Aybar, MD

12:30 - 12:40 A.M.

Preguntas y Respuestas

12:40 - 1:00 P.M.

Conferencia Magistral: de la Fisiología al Hospital Pediátrico Universitario
José E. Sifantes, MD
Catedrático en Pediatría
Hospital Pediátrico Universitario

Lunes, 22 de octubre - 7:30 P.M. - 10:50 P.M.

8:00 A.M.

Servicio Eucuménico Vestíbulo del Hospital

9:00 A.M.

Demostraciones de Especialidades en Enfermería

Martes, 23 de octubre - 7:30 A.M. - 4:30 P.M.

CASA ABIERTA
SESION DE ARCHIVOS Y EXHIBICIONES
ACTIVIDADES EDUCATIVAS DE DEPARTAMENTOS Y SECCIONES DE PEDIATRIA

RECEPCION ADMINISTRATIVA - SOCIAL
RECONOCIMIENTOS ESPECIALES
Club de la Facultad, Edificio de Farmacia, RCM

ACREDITADO 4 HORAS CATEGORIA I EDUCACION MEDICA CONTINUADA



LOS OBJETIVOS DE SALUD PARA ESTADOS UNIDOS EN 1990 Y SU APLICACION A PUERTO RICO.

II. Inmunizaciones

José G. Rigau Pérez, M.D., FAAP*

Resumen: De las diecinueve metas nacionales de salud para 1990 referentes a las enfermedades prevenibles por inmunización, cinco han sido aparentemente alcanzadas en Puerto Rico, diez están bajo estudio y/o siendo perseguidas, y cuatro necesitan trabajarse desde el plano más básico. La obtención de estos objetivos en Puerto Rico, al igual que en otros estados, exige la cooperación de diversas instituciones gubernamentales, académicas y cívicas.

En 1980 el Servicio de Salud Pública de los Estados Unidos ("U.S. Public Health Service") publicó unas metas para el mejoramiento de la salud de los habitantes del país en los próximos diez años.¹ Quince asuntos prioritarios fueron identificados: control de la hipertensión, planificación familiar, embarazos y salud infantil, inmunizaciones, enfermedades de transmisión sexual, control de agentes tóxicos, seguridad y salud ocupacional, prevención de accidentes y control de traumatismos, fluorización y salud dental, vigilancia y control de enfermedades infecciosas, fumar y el deterioro en la salud, abuso de alcohol y drogas, nutrición, condicionamiento físico y ejercicio, control de la tensión y el comportamiento violento. Dentro de cada área se especificaron los objetivos a alcanzar para 1990. Estos objetivos (226 en total), planteados de manera mensurable, se desarrollaron en consultoría con más de 500 expertos de los sectores público y privado, que representaban agencias de salud federales, estatales y locales, grupos de consumidores, organizaciones de voluntarios y profesionales de salud. Las metas se establecieron tomando en cuenta las tendencias actuales de factores pertinentes, tales como cambios demográficos, estilos de vida y la disponibilidad de fondos, y detallando lo que se asumió ocurriría con estos factores en la década de 1980 a 1990. Las metas han de alcanzarse por los esfuerzos de toda la gama de agencias e instituciones públicas y privadas, de personas y comunidades, y no se han establecido como una responsabilidad federal. El gobierno federal se ve llamado a dirigir, catalizar y respaldar un esfuerzo colectivo con móviles locales, y lleva a cabo evaluaciones periódicas del progreso hacia estos objetivos.^{2, 3}

Este artículo presenta la situación actual en Puerto Rico respecto a los objetivos relacionados con las enfermedades prevenibles por vacunación.

METODOS

Las metas aquí reseñadas fueron traducidas por el autor y se citan, en comillas, tal como aparecen en el texto original en inglés.¹ Se ha conservado, como en el original, el término "vacuna" para significar inmunización activa, aunque ninguno de los objetivos esté relacionado con la vacunación contra viruela. Cada meta se rotuló "AA", "P", o "I" de acuerdo con los siguientes criterios: AA (aparentemente alcanzada) si las estadísticas disponibles indican que el estado de la enfermedad o de la técnica de salud pública al momento actual en Puerto Rico concuerda con lo deseado para 1990; P (perseguida) si hay al momento un esfuerzo de recogida de datos respecto al problema y/o un programa establecido para el control de la enfermedad o prestación de servicio; I (indocumentada) si la información específica que estipula el objetivo no se conoce para Puerto Rico. Los datos de población se obtuvieron de la División de Recursos Humanos, Área de Planificación Económica y Social, de la Junta de Planificación de Puerto Rico. Las cifras indican el tamaño estimado de la población de Puerto Rico al primero de julio de cada año estudiado (1973 a 1983). Los datos de morbilidad provienen del Programa de Control de Enfermedades Transmisibles (hoy División de Epidemiología) del Departamento de Salud. Las cifras de morbilidad están presentadas por año calendario. Las tasas de morbilidad (por 100,000 habitantes) están calculadas usando la población total de Puerto Rico. Los datos de mortalidad se extrajeron de los análisis detallados inéditos que hace la Oficina de Estadísticas, Análisis y Control de Información (Administración de Facilidades y Servicios de Salud, Departamento de Salud) de los certificados de defunción que se cumplimentan cada año; los datos para 1982 y 1983 no estaban disponibles al momento de esta investigación. Hasta 1978 se usó la octava edición de la "International Classification of Diseases, Adapted for use in the United States" (ICDA-8), para identificar por números las causas de muerte, cambiando en 1979 a la nueva edición (ICDA-9).^{4, 5} Las rúbricas correspondientes a las enfermedades aquí estudiadas fueron las siguientes: difteria-032; tos ferina- 033; tétanos- 037; poliomiелitis aguda-

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040-43 (ICDA-8), 045 (ICDA-9); sarampión- 055; rubéola (sarampión alemán-056; paperas-072; síndrome de rubéola congénita- 761.3 (ICDA-8), 771.0 (ICDA-9). Las tasas por enfermedad en Estados Unidos se tomaron del "Annual summary 1982: reported morbidity and mortality in the United States", año disponible más reciente.⁶ Las metas para Puerto Rico en 1990 se calcularon manteniendo la proporción de las cifras con el tamaño de la población afectada. Aquellas metas expresadas como tasas se aplicaron, sin cambiar, a Puerto Rico. Las metas expresadas como números de casos fueron adaptadas a Puerto Rico utilizando un factor de conversión (población de Puerto Rico en el censo de 1980/ población censada de los 50 Estados Unidos = 3,196,520/ 226,545,805 = 0.014).

OBJETIVOS PARA 1990

Mejoramiento del estado de salud

a. "Para 1990 la incidencia testimoniada de sarampión común debe reducirse a menos de 500 casos por año - todos importados o a no más de dos generaciones después de la importación." - P

Este objetivo implica la erradicación del sarampión común y señala que la meta, proporcional a la población local, consiste en menos de 7 casos de sarampión por año, adjudicables a la importación de la enfermedad. Los casos de sarampión han disminuido en un 95% desde 1973 (tabla 1), pero todavía Puerto Rico tuvo en 1983 una incidencia cuatro veces más alta que la incidencia de la enfermedad en Estados Unidos. Hay que considerar que los casos declarados en Puerto Rico han tenido un diagnóstico exclusivamente clínico hasta finalizar el 1982. Es indudable que un buen número de casos notificados como sarampión consiste en realidad de otras enfermedades exantemáticas. Esta sospecha la respaldan los datos sobre paperas (ver abajo), enfermedad cuyo diagnóstico clínico es más preciso que el de sarampión y en la cual el efecto de la campaña de inmunización del Departamento es evidente.

Tabla 1

Sarampión en Puerto Rico, 1973-83

Año	Muertes	Casos	Población Total	Tasa de incidencia por 100,000 habitantes
1973	2	2,021	2,872,300	70
1974	1	679	2,890,000	23
1975	0	830	2,938,800	28
1976	0	589	3,018,300	20
1977	1	1,164	3,074,100	38
1978	0	326	3,121,600	10
1979	1	434	3,160,700	14
1980	0	231	3,206,900	7
1981	1	340	3,246,800	10
1982		224	3,263,273	7
1983		95	3,266,900	3

Tasa Estados Unidos 1982

0.7

Meta Puerto Rico 1990

7 casos

b. "Para 1990 la incidencia testimoniada de paperas debe reducirse a menos de 1,000 casos por año." - P

El objetivo proporcional a la población de Puerto Rico es de menos de 14 casos por año. La incidencia de paperas en la isla disminuyó grandemente de 1978 a 1979 (tabla 2), simultáneamente con la implantación de la decisión del Departamento de Salud de exigir la vacuna de paperas a los entrantes a escuela y, a la vez, de proveer la vacuna en sus clínicas. Esta vacuna tardó en ofrecerse por ser la más cara de las vacunas infantiles (\$3.23 la dosis, al precio que consigue el Departamento con subsidio federal, contra \$2.27 la dosis de sarampión común, la segunda más cara entre estas vacunas). Actualmente la tasa de incidencia notificada en Puerto Rico es el doble que en Estados Unidos.

c. "Para 1990 la incidencia testimoniada de sarampión alemán (rubéola, "rubella" en inglés) debe reducirse a menos de 1,000 casos por año." - AA

El objetivo proporcional a la población local es de menos de 14 casos por año. Los números, muy bajos, que señalan las estadísticas de vigilancia epidemiológica (tabla 3) pueden estar afectados por un sesgo en el sistema, pues hay escasez de facilidades para el diagnóstico serológico. Los síntomas de la enfermedad son efímeros y poco específicos, y pueden confundirse con los de dengue o influenza. No hay que olvidar, además, que la rubéola acusa una incidencia más baja en poblaciones tropicales isleñas que en las continentales de zona templada.⁷

d. "Para 1990 la incidencia testimoniada del síndrome de rubéola congénita debe reducirse a menos de 10 casos por año." - AA

Aplicado a la población de Puerto Rico, este objetivo proyecta la prevención de todos los casos del síndrome de rubéola congénita. El sistema de vigilancia en vigor sólo señala tres casos de 1973 a 1983: un caso en 1975 y dos en 1978. No hay muertes notificadas en ese período causadas por este síndrome. La exactitud de estos datos es debatible, por las razones señaladas arriba.

e. "Para 1990 la incidencia testimoniada de difteria debe reducirse a menos de 50 casos por año." - AA

Para Puerto Rico esta meta señala un caso de difteria por año. En la década pasada se declararon tres casos de la enfermedad (uno en 1974 y dos en 1976, ninguno de ellos confirmado rigurosamente por laboratorio) y no hubo ninguna muerte. Es poco probable que estén ocurriendo casos de difteria en Puerto Rico y no sean notificados, así que este objetivo puede darse por conseguido.

f. "Para 1990 la incidencia testimoniada de tos ferina debe reducirse a menos de 1,000 casos por año." - P

Los casos declarados en los últimos dos años están sobre la meta local para 1990 (14 casos por año - ver tabla 4). La tasa de incidencia de la enfermedad en Puerto Rico es 56% menor que en los Estados Unidos.

g. "Para 1990 la incidencia testimoniada de tétanos debe reducirse a menos de 50 casos por año." - P

La meta toleraría un caso de tétanos por año en Puerto Rico. Para conseguirla, y reducir la tasa de incidencia local, cuatro veces mayor que la de los Estados Unidos (tabla 5), habrá que concentrar los esfuerzos de vacunación en la población de edad madura. Repetidos estudios señalan que a mayor edad, mayor proporción de la población de edad avanzada carece de niveles adecuados de protección contra tétanos.⁸

h. "Para 1990 la incidencia testimoniada de polio debe reducirse a menos de 10 casos por año." - AA

Este objetivo proyecta la prevención de todos los casos de polio en Puerto Rico. El único caso de la década fue notificado en 1974. Se han registrado, sin embargo, nueve muertes (tres en 1973, dos en 1976, una en 1979, otra en 1980 y dos en 1981) de lo que, según la rúbrica ICDA es poliomiélitis aguda. Además de la posibilidad de que estas defunciones ocurrieran en personas con secuelas de polio y no polio aguda, es posible que procesos neurotróficos virales causados por virus diferentes al polio fueran responsables de estos casos. En ausencia de facilidades de diagnóstico de laboratorio virológico es imposible distinguir entre los virus que producen manifestaciones clínicas muy similares.

Tabla 2

Paperas en Puerto Rico, 1973-83

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	0	1,117	39
1974	0	1,284	44
1975	0	1,265	43
1976	0	918	30
1977	0	1,104	36
1978	0	1,718	55
1979	0	604	19
1980	0	177	6
1981	0	158	5
1982		103	3
1983		146	4
Tasa Estados Unidos 1982			2
Meta Puerto Rico 1990			14

Tabla 3

Sarampión Alemán (Rubéola) en Puerto Rico, 1973-83

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	0	42	1.46
1974	0	35	1.21
1975	0	16	.54
1976	0	26	.86
1977	0	39	1.27
1978	0	17	.54
1979	0	41	1.30
1980	1	30	.94
1981	0	3	.09
1982		13	.40
1983		9	.28
Tasa Estados Unidos 1982			1.0
Meta Puerto Rico 1990			14

Tabla 4

Tos Ferina en Puerto Rico, 1973-83

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	0	26	.91
1974	0	37	1.28
1975	2	158	5.38
1976	0	43	1.42
1977	1	32	1.04
1978	0	21	.67
1979	0	6	.19
1980	1	14	.44
1981	0	22	.68
1982		22	.67
1983		15	.46
Tasa Estados Unidos 1982			.82
Meta Puerto Rico 1990			14

Tabla 5

Tétanos en Puerto Rico, 1973-83

Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	10	11	.38
1974	3	7	.24
1975	12	19	.65
1976	8	10	.33
1977	10	12	.39
1978	10	11	.35
1979	9	11	.35
1980	10	15	.47
1981	5	7	.22
1982		6	.18
1983		6	.18
Tasa Estados Unidos 1982			.04
Meta Puerto Rico 1990			1

Mayor concientización pública y profesional

i. "Para 1990 todas las madres de recién nacidos deben recibir instrucción sobre el programa de inmunizaciones para sus bebés antes de salir del hospital o después de dar a luz en su hogar." - P

No hay datos de referencia disponibles para Puerto Rico. La implantación general de esta práctica en los hospitales cubriría el 99.3% de los nacimientos.⁹ Desde 1974 se entrega el itinerario de vacunación a los padres, impreso en la misma hoja que el certificado de nacimiento. Ellos, en su afán por conservar el certificado en lugar seguro, omitían presentarlo en las clínicas de vacunación. Al presente se les entrega también un record para las inmunizaciones en hoja separada del certificado de nacimiento del infante.

Mejoramiento en los servicios y la protección

j. "Para 1990 por lo menos el 90% de todos los niños deben haber completado su serie de inmunizaciones

básicas a la edad de dos años - sarampión común, paperas, rubéola, polio, difteria, tos ferina y tétanos. (En 1978, el cumplimiento variaba de 50 a 90%)” - P

En 1983 el Programa de Inmunización examinó los expedientes de inmunización de 10,735 niños de edad 2 meses a 24 meses, en 21 clínicas públicas escogidas al azar de entre todas las de la isla (este número representó el 13% de todos los niños de esta edad atendidos en clínicas públicas). Se encontró gran variación en la cobertura de inmunización (ajustada a la edad) entre las distintas clínicas. En general, solo 35% de los expedientes examinados indican que el niño hubiera recibido las vacunaciones apropiadas para su edad.

k. “Para 1990 al menos 95% de los niños que asisten a facilidades acreditadas de cuidado diurno, y de kindergarten a cuarto año de escuela superior deben haber recibido todas las inmunizaciones recomendadas para su edad.” - P

La ley 235 del 23 de julio de 1974 hizo compulsorias las inmunizaciones prescritas por el Secretario de Salud en los menores de edad que comenzaran a cursar estudios en un kindergarten o primer grado de cualquier escuela en Puerto Rico. Con su implantación se consiguió elevar la proporción de entrantes a escuela adecuadamente inmunizados contra difteria, tétanos, tos ferina, polio, sarampión común y rubéola, de cerca de 27% en el año escolar 1975-76 a 93% en el 1982-83. La cobertura para paperas aumentó de 49% en el año lectivo 1979-80 a 86% en el 1982-83. Para alcanzar el objetivo aquí señalado, se presentó un proyecto de ley ante la Asamblea Legislativa, mediante el cual se establecía como requisito de admisión a cualquier escuela y universidad en Puerto Rico, para cualquier estudiante menor de 21 años, el estar debidamente inmunizado de acuerdo a los criterios establecidos por el Departamento de Salud. Este proyecto derogó la ley 235 (de 1974) y se convirtió en la ley 25 del 25 de septiembre de 1983. Cerca de 500,000 personas fueron vacunadas en el verano de 1984 para cumplir con la ley. Esto hará aumentar la cobertura inmunitaria en los niños que entraron al primer año de escuela antes de 1975 y que ahora son adolescentes.

l. “Para 1990 al menos 60% de las poblaciones de alto riesgo, según definidas por el Comité consultor sobre prácticas de inmunización (CCPI) del ‘U.S. Public Health Service’ debe estar recibiendo inmunizaciones anuales contra influenza.” - I

No hay datos de referencia para la cobertura vacunal contra influenza en las poblaciones a riesgo en Puerto Rico. El Departamento de Salud distribuye una pequeña cantidad de dosis cada año. Se desconoce la frecuencia con que los médicos privados administran la vacuna a sus pacientes.

m. “Para 1990 al menos 60% de las poblaciones de alto riesgo, según definidas por el CCPI, debe haber inmunización contra pulmonía neumocócica.” - I

Tampoco hay datos de referencia para la cobertura vacunal contra neumococos en las poblaciones a riesgo en Puerto Rico. El Departamento de Salud no distribuye esta vacuna y se desconoce la frecuencia de su uso por los médicos privados.

n. “Para 1990 al menos 50% de las personas en poblaciones señaladas por el CCPI deben estar inmunizadas con nuevas vacunas autorizadas para uso clínico rutinario, dentro de los cinco años después del licenciamiento de cada vacuna.

Nota: Este mismo objetivo también se asignó al área de vigilancia y control de enfermedades infecciosas (I.h). Entre las candidatas a nuevas vacunas se encuentran la de hepatitis A, otitis media (*S. pneumoniae* y *H. influenza*), algunos virus entéricos y respiratorios, y meningitis (*N. meningitidis* grupo B, *S. pneumoniae*, *H. influenza*).” - I

Este objetivo sólo puede estimarse usando los datos disponibles para las vacunas lanzadas al mercado más recientemente, la de neumococos (1977) y la de hepatitis B (1982). El Departamento de Salud no las ha incorporado todavía a su programa de inmunizaciones. Lo mismo puede decirse de la mayoría de los hospitales y médicos privados, aquí y en el continente.

o. “Para 1985 los Estados Unidos deben tener establecido un plan para activar programas de inmunización en masa en caso de posible epidemia de influenza o de otra enfermedad epidémica para la cual haya vacuna.” - AA

La iniciativa para este objetivo está fuera de las atribuciones de las autoridades de Puerto Rico. La campaña de vacunación del verano de 1984 ha confirmado que el Departamento de Salud de Puerto Rico cuenta con personal adiestrado y facilidades para almacenaje y administración de vacuna en toda la isla.

p. “Para 1990 ninguna póliza abarcadora de seguros de salud debe excluir inmunizaciones. (No hay datos de referencia disponibles.)” - I

Los planes de seguro médico que cubren, entre sus servicios, las inmunizaciones, son muy escasos, la excepción más que la regla.

Mejoramiento en los servicios de vigilancia y evaluación

q. “Para 1990 al menos 95% de todos los jóvenes hasta la edad de 18 años (inclusive) deben tener al día su expediente oficial de inmunización, en un formato uniforme que utilice criterios uniformes para completar las inmunizaciones. (No hay datos de referencia disponibles.)” - P

Desde 1974 el Departamento de Salud está usando el mismo record oficial de vacunación para los niños atendidos en sus agencias en todo Puerto Rico. Está en planes suministrarle la misma forma a los médicos privados, para que así todos los niños tengan expedientes en el mismo formato. Por disposición de la ley 25 (1983), el record de inmunización del estudiante, provisto por el Departamento de Salud, será igual en todas las escuelas de Puerto Rico.

r. “Para 1990 los sistemas de vigilancia epidemiológica de enfermedades infantiles prevenibles por vacunación deben haber mejorado como para que 1) al menos 90% de los casos hospitalizados y 50% de los no hospitalizados sean notificados, y 2) se utilicen definiciones uniformes de caso a través de los Estados Unidos. (No hay datos de referencia disponibles.)” - P

No hay tampoco datos de referencia sobre la sensibilidad del sistema de vigilancia para los casos hospitali-

zados y los no hospitalizados. La definición de caso de sarampión común que se usa en Puerto Rico es la misma que se ha establecido uniformemente en los Estados Unidos.

Discusión

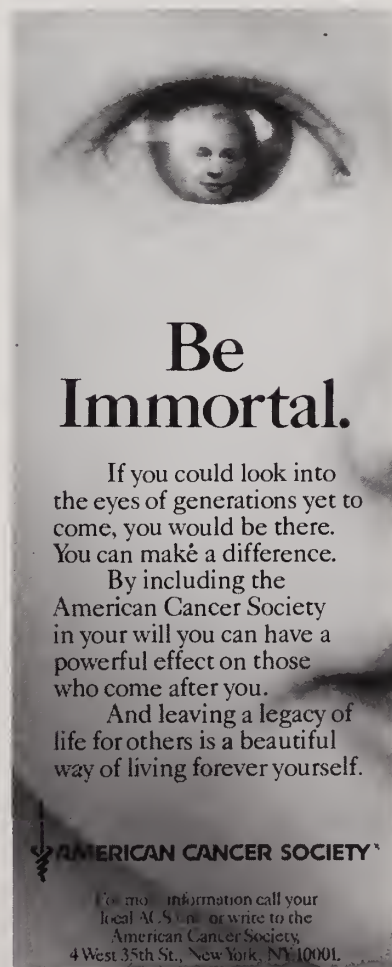
De los 19 objetivos presentados, cinco objetivos están aparentemente alcanzados ("AA" - 26%): incidencia testimoniada de sarampión alemán (rubéola o "rubella") menor de catorce casos por año, ni un solo caso por año del síndrome de rubéola congénita, de difteria o de polio; y la existencia de un sistema para activar rápidamente programas de inmunización en masa. Sin embargo, hay que hacer énfasis en que los datos recogidos para rubéola congénita son muy poco fiables y presentan una imagen falsa de la frecuencia de estas enfermedades en Puerto Rico. Para alcanzar los 10 objetivos rotulados "P" (aquellos para los cuales hay al momento un esfuerzo de recogida de datos y/o un programa establecido para el control de la enfermedad o prestación del servicio) el Departamento de Salud está asignando personal y cantidades considerables de fondos estatales y federales al Programa de Inmunización de la Secretaría Auxiliar para Mantenimiento de la Salud. Otro objetivo quizás sea alcanzado en 1984: la reducción de casos de tos ferina a menos de 14 por año parece ser inminente. La implantación de la ley 25 de 1983 creó una demanda enorme de inmunizaciones para que los estudiantes pudieran entrar a la escuela en agosto de 1984. De esta manera la población juvenil estará casi totalmente protegida contra las enfermedades prevenibles por vacunación. Quedan todavía dos grupos de edad que no se verán beneficiados por la nueva ley: los menores de cuatro años y los mayores de veintiuno. La incidencia de tétanos no disminuirá hasta que no mejore la cobertura inmunitaria en la población adulta. Los cuatro temas u objetivos para los cuales no hay la información básica para proceder ("I") son sumamente inquietantes, pues apuntan a dos problemas muy difíciles de resolver: cómo conseguir la inclusión de servicios de medicina preventiva en los seguros médicos, y cómo conseguir que los médicos y las clínicas incorporen a su práctica rutinaria la administración de esos servicios, especialmente los más novedosos.

El primer artículo de esta serie examinó los objetivos relacionados con la vigilancia y control de las enfermedades infecciosas.¹⁰ El próximo artículo reseñará los objetivos relacionados con las enfermedades de transmisión sexual.

Abstract: Of the nineteen national health goals for 1990 alluding to diseases that can be prevented by immunization, five have already been apparently achieved in Puerto Rico, ten are under study and/or being pursued, and four need to be developed from the very basic stages. The achievement of these objectives in Puerto Rico, as in other states, requires the cooperation of many governmental, academic and voluntary institutions.

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What can you do for hypertensives like Laura K?



Noncompliant

Frequently misses one or more of her three daily pills.

Lives alone

Doesn't cook much "from scratch." Eats mostly processed foods.

Worsening

Controlled at last visit but now her diastolic reads 101 mmHg... age 64.

Depressed

Sleeps badly and sometimes has bad dreams.

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Laura K represents 5,335 women between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Few CNS effects

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN—making it an excellent choice for patients like Laura K, who may experience CNS effects with other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Laura K...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary
prescribing information.



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN® (atenolol)

For Laura K...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (tree base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1–2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100–150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15–35	16–27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on file, Stuart Pharmaceuticals. 2. Herman RL, Lamdin E, Fischetti JL, Ko HK: Postmarketing evaluation of atenolol (Tenormin®). A new cardioselective beta-blocker. *Curr Ther Res* 1983; 33(1):165–171. 3. Zacharias FJ: Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980; 6(suppl 1):86–89.



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ESTUDIOS CLINICOS

Conservative Repair of the Mitral and Tricuspid Valves: Eight Years Experience with Duran Flexible Ring Annuloplasty

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Carlos M. G. Duran, M.D., Ph.D.

Summary: The modern concept of annuloplasty has made reconstructive surgery of the mitral and tricuspid valves a safe and reproducible technique. This study describes the 8 year-follow-up experience with the Duran Flexible Ring Annuloplasty in the mitral and tricuspid positions in two institutions.

The conservative mitral surgical techniques performed in the 290 patients of the mitral group includes: 240 mitral commissurotomy (82.7%), 144 papillary muscle splittings (49.6%), 39 chordal shortenings (13.4%), and 22 leaflet repairs (7.5%). Concomitant surgery to the aortic and/or tricuspid valve was performed in 146 patients. All patients with isolated open mitral commissurotomy or other types of mitral annuloplasty were excluded from this study. Hospital mortality was 3.4% (10 cases) and the linearized incidence of late mortality was 0.95% patient-years. Cumulative duration follow-up was 1,104 patient-years. Ninety-seven percent of patients are in New York Heart Association Functional Class I-II postoperatively. Linearized incidence of postoperative thromboembolism was 3.6% patient-years. Fifteen patients (5.6%) required reoperation; the actuarial curve of patients free of reoperation at 8 years was 92.6%.

The group of patients undergoing conservative tricuspid surgery includes 403 patients, 170 cases also required tricuspid commissurotomy. The tricuspid valve showed an organic lesion in 198 patients (49.2%) and a functional lesion in 205 patients (50.8%). The hospital mortality of patients undergoing tricuspid valve surgery was 9.6% (39 patients) and the late mortality 6.2% (22 patients). Cumulative duration follow-up was 1,401.3 patient-years. Ninety-six percent of patients are in New York Heart Association Functional Class I-II postoperatively.

In this study we emphasize the importance of knowing the normal and pathologic anatomy of the mitral and tricuspid valves. We also stress the importance of adequate atrial and valvular exposure, the use of appropriate instruments and

our understanding of the different conservative techniques to achieve results superior to those of valvular replacement.

Although there have been significant advances in the construction and design of cardiac valve prostheses, prosthetic replacement of the mitral and tricuspid valve are still considered palliative surgical procedures.

Mechanical prostheses are plagued by the problems of mechanical failure and thromboembolism, but their durability is supposedly unlimited.

Modern conservative surgery of the atrio-ventricular valves was pioneered by Lillehei.¹ Satisfactory results were described by Merendino,² Kay,³ Wooler,⁴ and Reed.⁵ However, those conservative valvular techniques were not extensively accepted because repair was thought to be more complicated, and to have more unpredictable long-term results, than the first truly successful prosthesis, the Starr-Edwards valve.

Safer techniques of extracorporeal circulation and myocardial protection, and the modern concept of anatomical annuloplasty described by Carpentier⁶ and Duran,⁷ made reconstructive valve surgery a safer treatment for patients with mitral and tricuspid valve disease. The encouraging results obtained, together with the disappointing long-term results of mechanical valves or bioprosthesis rekindled the interest in conservative repair of the atrioventricular valves.

Furthermore, our particular interest in conservative repair was further encouraged because the majority of our patients came from an extensive geographical area where adequate monitoring of the anticoagulation status is practically impossible.

This manuscript summarizes our experience with 290 patients with mitral annuloplasty and 403 patients with tricuspid annuloplasty using the Duran flexible ring.*

MITRAL VALVE

Indications for Conservative Repair

A very thorough pre-operative assessment is mandatory in all patients on whom one contemplates valvular repair.

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**Duran Flexible Ring - Hancock Laboratories, 4633 East La Palma, Anaheim, California - 92807.*

This includes non-invasive cardiovascular tests, and a complete hemodynamic, angiographic study with bi-ventriculography.

Conservative repair is possible in rheumatic, congenital, ischemic, and degenerative valvulopathies. It is equally satisfactory in lesions of restricted or increased leaflet mobility.

For the purposes of simplification, we classify diseased mitral valves into "good quality" and "poor quality": Table I.

A "good quality" mitral valve is one whose leaflets are pliable, slightly or moderately fibrosed, non-calcified, with minimal or moderate deformity of the subvalvular apparatus.

A "poor quality" mitral valve, not amenable to conservative repair, is one with severely fibrotic and immobile leaflets, massive calcification, or severely deformed subvalvular apparatus.

For patients in New York Heart Association (NYHA) Functional Class II operation is recommended only when conservative repair, rather than valve replacement, is anticipated. Patients in NYHA Functional Class III and IV are considered candidates for conservative repair or replacement.

TABLE I

Mitral Valve Conservative Repair		
INDICATIONS: Pathology		
Quality	Good	Poor
LEAFLET		
Pliability	++	-
Fibrosis	+	++
Calcification	+	++
SUBVALVULAR APP.		
Deformity	+	++
Fibrosis	+	++

TECHNIQUES OF REPAIR OF THE MITRAL VALVE

Cardiopulmonary Support

The operations are done through a median sternotomy. Cannulae, preferably right angled, are inserted into the superior and inferior venae cavae. Ascending aortic cannulation is performed as previously described.⁸ The left ventricle is sumped via the apex of the heart using a circuit that will allow testing of the mitral valve.⁹ After the aorta is cross clamped 750 ml of crystalloid cardioplegic solution is infused through the aortic root. A bolus of 250 mls of blood cardioplegia (ph 7.8) is infused every 30 minutes after cross clamping. The pericardial sac is initially irrigated with cold, 4°C, Ringer's lactate solution and myocardial hypothermia is maintained by the Shumway technique¹⁰ or a Topical Cooling Device R¹¹ (TCD).

A remnant of Ringer's lactate (approximately 25% of the pericardial capacity) is left when the TCD is utilized.

Anatomy of the Mitral Valve

The mitral annulus is the fibrous thickening of the superior border of the left ventricular myocardium that extends from the right to the left fibrous trigones. The annulus is horseshoe-shaped and is in close relationship

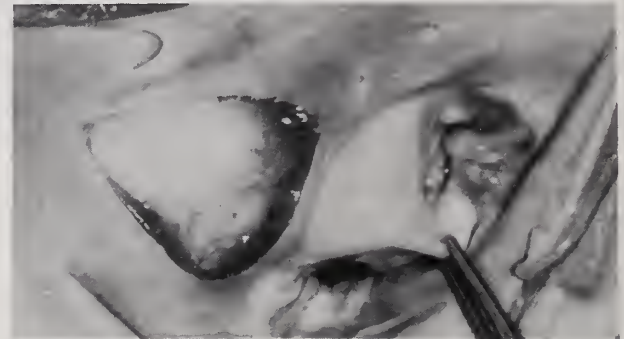


Figure 1. Relationship between the anterior mitral leaflet (A) and the aortic annulus. A segment of the left atrial wall (LA) has been removed to illustrate the proximity of the wall of the aorta. Traction on the anterior leaflet of the mitral valve, demonstrates the aortic fibrous trigones (T). P= Posterior mitral leaflet.

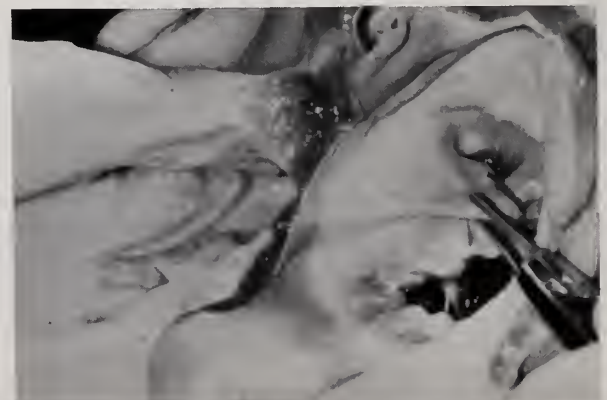
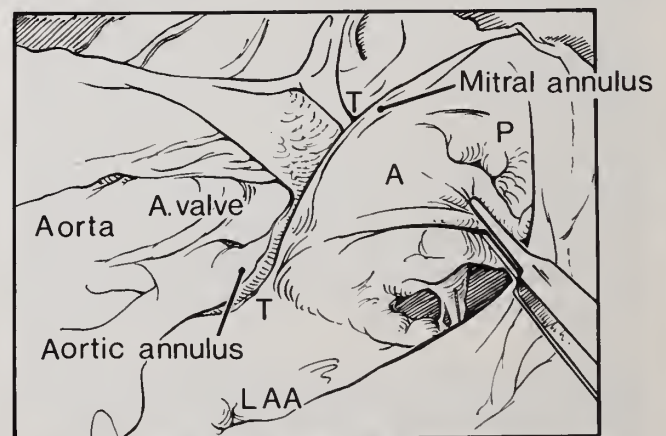


Figure 2. Relationship of the aortic valve, aortic annulus and mitral valve. A segment of left atrium and a segment of the wall of the aorta have been removed. LAA = Left atrial appendage.

with the aortic root (Figs. 1 and 2). The intertrigonal portion of the annulus is non-distensible and represents approximately one third of the circumference. This annulus serves as support for the insertion of the posterior leaflet, and plays an important role in mitral valve competence. Laboratory studies have demonstrated "sphincter-like" movement of the mitral annulus that can reduce the mitral orifice area between 20 to 40 percent.^{12, 13, 14}

There are two mitral leaflets, the anterior and posterior (Fig. 3). The anterior leaflet is almost four times the size of the posterior leaflet¹⁶ Figure 4 shows a graphic representation of the various chordae tendinae of the mitral valve. Marginal chordae ("ma") are those that insert in the free edge of the leaflet, basal chordae ("b") are those that insert in the junction of the leaflet with the ventricular wall. Medial ("m") chordae are those which adhere to the inferior (ventricular) surface of the leaflet between the insertion of the marginal and basal chordae. The function of the chordae is to maintain competence during systole and the valve open during diastole.

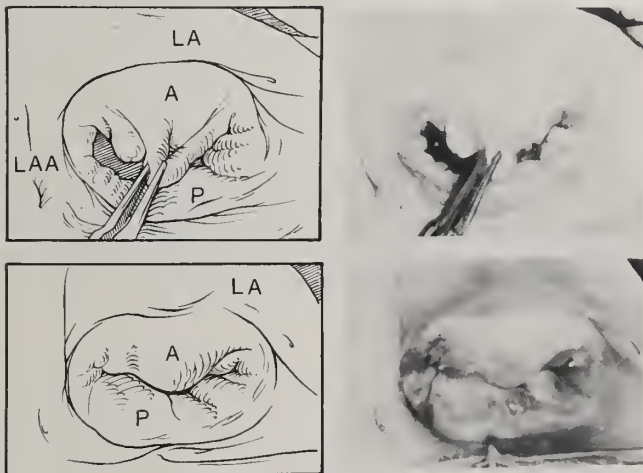


Figure 3. The mitral leaflets. The superior figure demonstrates the furrow created by placing traction on the anterior mitral leaflet (A) which point towards fibrous trigone. The lower figure shows the leaflets in the closed position.

The mitral subvalvular apparatus includes the anterior and posterior papillary muscles (Fig. 5). The anterior papillary muscle has chordae tendinae that insert in the anterior half of both the anterior and posterior leaflets. From the posterior papillary muscle, the chordae originate which insert in the posterior half of the anterior and posterior leaflets. Thus each papillary muscle gives off chordae that insert in both leaflets (Fig. 6).

The left ventricular wall plays a very important role in the physiology of mitral valve closure. Recent laboratory experiments in patients without myocardial disease have demonstrated that an increase in left ventricular volume greater than 150 ml/m² can result in mitral insufficiency without annular dilatation, this is thought to be due to the displacement of the valvular apparatus by the increase in size of the cavity.¹⁶ Ischemic and degenerative processes can affect the properties of the myocardial fibers next to the subvalvular apparatus and may result in mitral insufficiency.

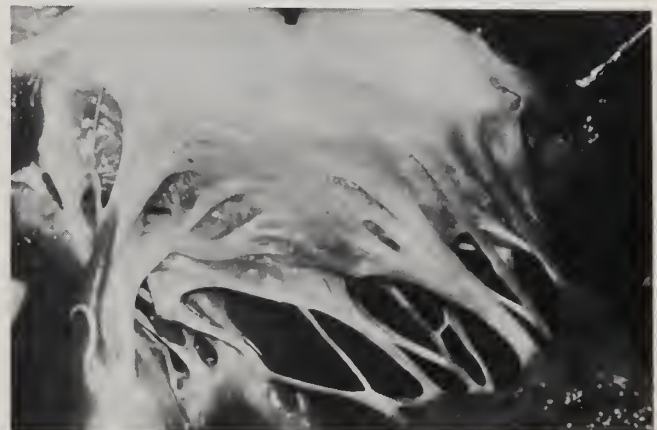
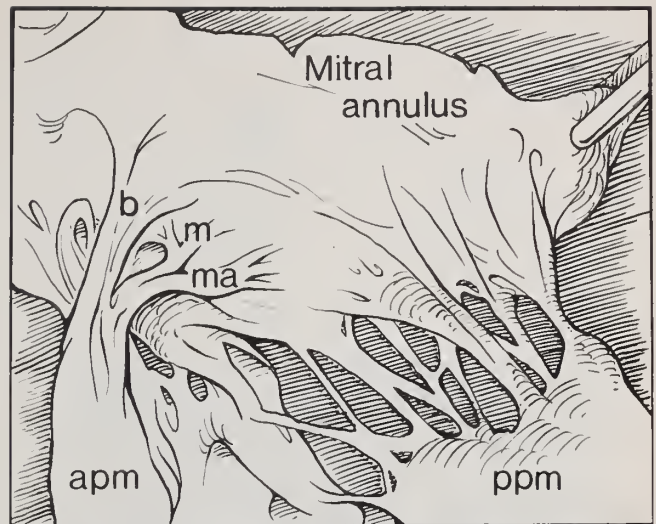


Figure 4. The subvalvular mechanism of the mitral valve. Marginal chordae (ma) insert in the free border of the leaflet. Basal chordae (b) are those that insert in the junction of the leaflet and the ventricular wall. medial chordae (m) insert in the inferior surface between the insertion of the marginal basal chordae. apm = anterior papillary muscle; ppm = posterior papillary muscle.

Exposure of the Left Atrium and Mitral Valve

Mitral valve reconstructive procedures require ample exposure of the left atrial cavity, the mitral valve and the subvalvular apparatus. A very wide left atriotomy is performed (Fig. 7). The initial incision is done immediately in front of the right superior pulmonary vein and is extended cephalad under the superior vena cava. Caudally, the atriotomy is extended in front of the right inferior pulmonary vein and well under the inferior vena cava. It is crucial that the anatomical space between the left atrial wall and the inferior aspect of the inferior vena cava can be developed and exposed. In this manner the left atrium can be widely opened to within 1.5 cms from the mitral annulus. Special left atrial retractors* are inserted into the atrium (Fig. 8). The mitral valve should lie exactly in the middle of the operative field in order to visualize the mitral leaflets, commissures and subvalvular mechanism. An inadequate left atrial incision will place

*Revuelta-Garcia Set for Mitral and Tricuspid Valve Repair. Pilling Instruments. Narco Scientific, Pilling Division. 420 Delaware Drive. Fort Washington, PA - 19034.

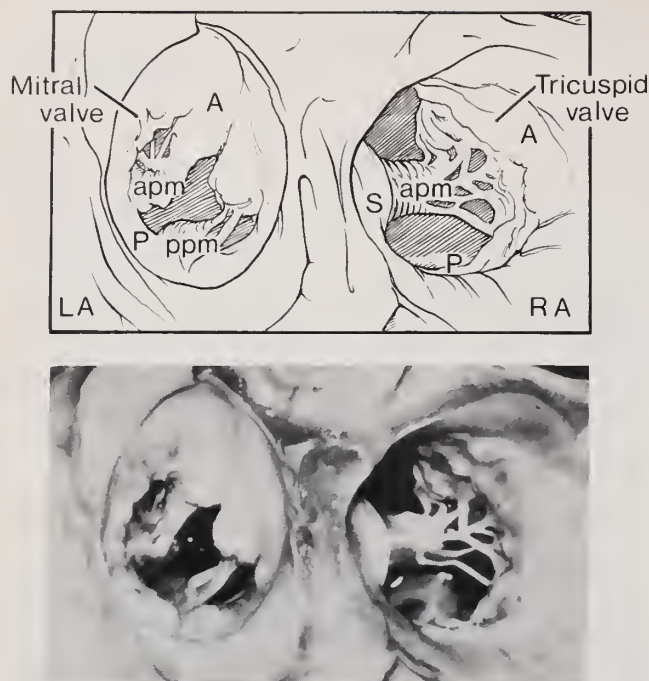


Figure 5. The subvalvular apparatus of the mitral and tricuspid valves. The upper part of both atria and most of the interatrial septum have been removed. The close relationship between the mitral and tricuspid valves can be appreciated. The papillary muscles can be visualized. A = anterior leaflet. P = posterior leaflet. S = septal leaflet. apm = anterior papillary muscle. ppm = posterior papillary muscle; LA = left atrium. RA = right atrium.

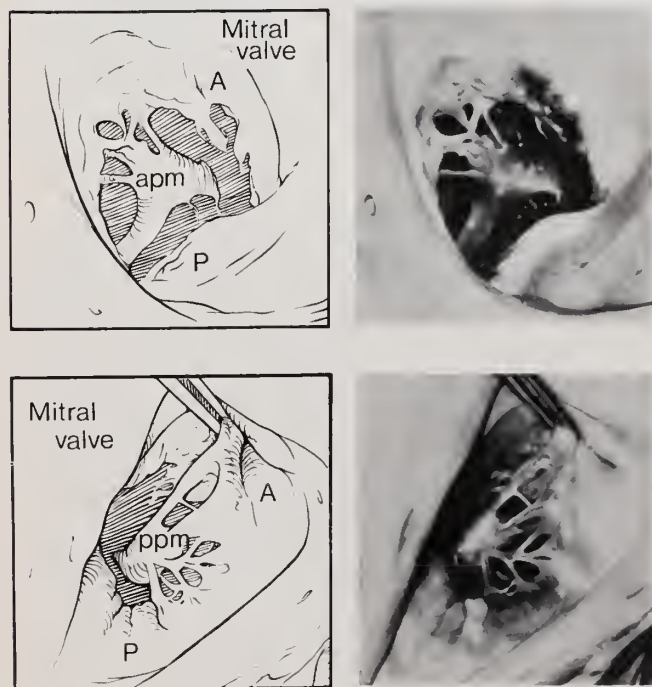


Figure 6. The subvalvular mechanism of the mitral valve. The relationship of the anterior (apm) and posterior (ppm) papillary muscles. Both papillary muscles contribute chordae to each leaflet. A = anterior leaflet. P = posterior leaflet.

the mitral valve too far inferior in the operative field or too far under the right atrium, thus making appropriate repair practically impossible due to poor visualization.

The techniques for mitral valve conservative repair are basically:

- Commissurotomy
- Ring Annuloplasty
- Leaflet, Chordal or Papillary Muscle Repair

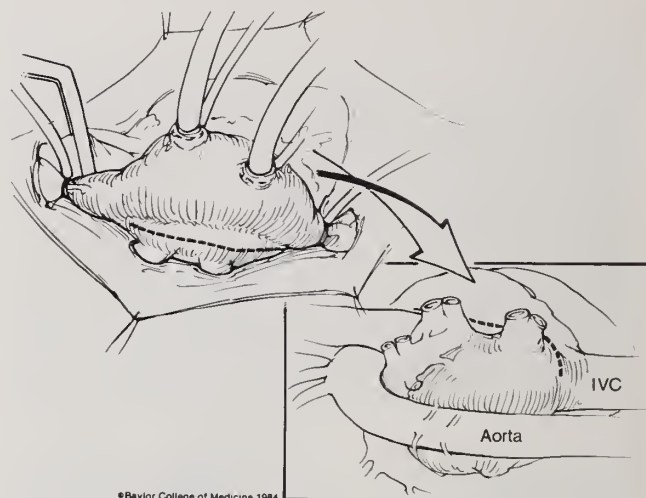


Figure 7. Exposure of the mitral valve. A wide left atriotomy is done by incising the left atrium in front of the right superior pulmonary vein. The incision (dotted line) is extended cephalad under the superior vena cava, and inferiorly under the inferior vena cava. It is imperative to develop the virtual space between the inferior vena cava and the left atrium.

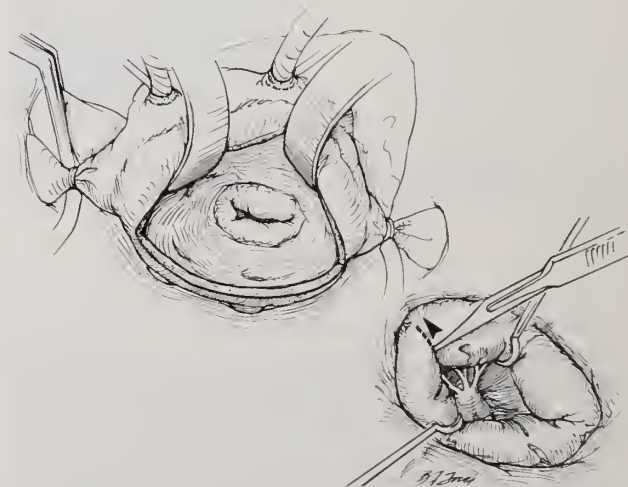


Figure 8. Exposure of the mitral valve - continued. The mitral valve should lie in the middle of the field. Valvular hooks are introduced to study the subvalvular apparatus. Anterior commissurotomy is performed.

Isolated Mitral Stenosis

Mitral stenosis is due to fusion of the valve commissures with or without involvement of the chordae tendineae or the papillary muscles. It is important to recognize the degree of involvement of the three components in order to accomplish an adequate repair.

Once the mitral valve has been exposed, special hooks are utilized for the repair (Fig. 8). The hooks are deliberately caught on the free aspect of the leaflets and looped on the marginal chordae to place traction on the leaflets. This maneuver usually delineates the commissures and furthermore, helps expose the subvalvular mechanism. The anterior commissure is usually opened first. A valvular mirror is inserted under the leaflets to visualize better the commissure and the relationship of the chordae. The leaflets are opened with a #11 blade avoiding division of the marginal chordae. If there is involvement of the subvalvular mechanism, its repair is done next. The chordae are separated and divided if necessary. In many cases the anterior papillary muscles must be split (Fig. 9). It is very important to avoid dividing the origin of the primary chordae from the papillary muscle. Once the superior split of the papillary muscle is performed, the knife is turned and with the spatula end, the incision is extended deeper into the papillary muscle to within one centimeter from the left ventricular wall. The papillary muscles, the chordae, leaflets and subvalvular mechanism are carefully inspected with the mirror. The same maneuvers are repeated for the posterior commissurotomy. However, in certain cases it is preferable to start the division of the commissure at the lateral aspect, that is, close to the annulus. This is a point of maximum separation of the primary chordae, consequently, there is less opportunity of damage. An opening in this area allows light to enter the subvalvular area to better visualize the chordae and the papillary muscle.

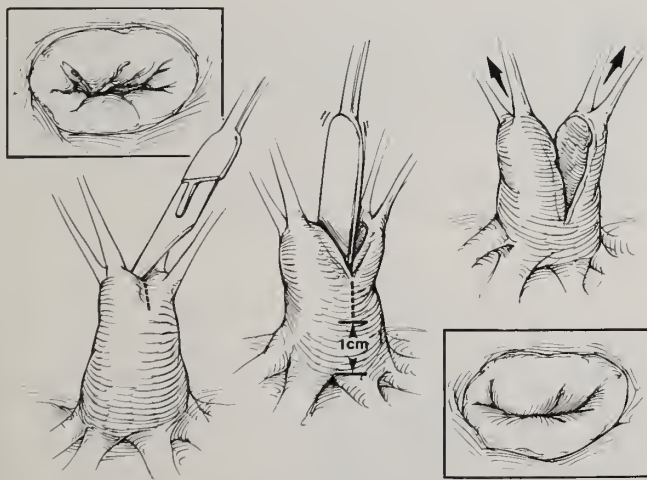


Figure 9. Splitting of a papillary muscle. An incision is made in the tip of the papillary muscle carefully avoiding the origin of the chordae. The split is extended to within 1 cm of the left ventricular wall with the spatula end of the knife handle. This allows ample movement of the subvalvular mechanism and wide opening of the valve.

Radical mitral commissurotomy requires intraoperative testing to insure the adequacy of the repair. Figure 10 illustrates the modified circuit which has been utilized to test for mitral valve competence. A sidearm of the arterial perfusion line is connected to the line which is used as a sump from the left ventricle. By the relocation of a clamp,

blood under pressure is allowed to enter into the left ventricular cavity. This maneuver distends the left ventricle and the repaired valve. A small amount of mitral insufficiency is considered acceptable and well tolerated by the patient. Significant resultant mitral regurgitation can usually be treated by ring annuloplasty particularly if the leak is at the commissural edge. Selective annular reduction at this point usually eliminates mitral regurgitation. This method of testing of the mitral valve repair has been utilized in over 1000 cases with excellent correlation between the intra-operative findings and post-operative hemodynamic and angiographic studies.⁹

Mitral stenosis can be accompanied by the deposition of calcium nodules particularly in the commissural areas. The presence of calcification by itself does not preclude an attempt to repair a diseased mitral valve. The commissure must be widely opened, the leaflets retracted and the nodule excised with a small cup type rongeur. When this is performed, the leaflet has to be carefully inspected both in the superior and inferior aspect to be sure there are no dents on the leaflet. It is also important not to damage the primary chordae. If a commissural gap would result, selective annular reduction can be performed to preserve the mitral valve.

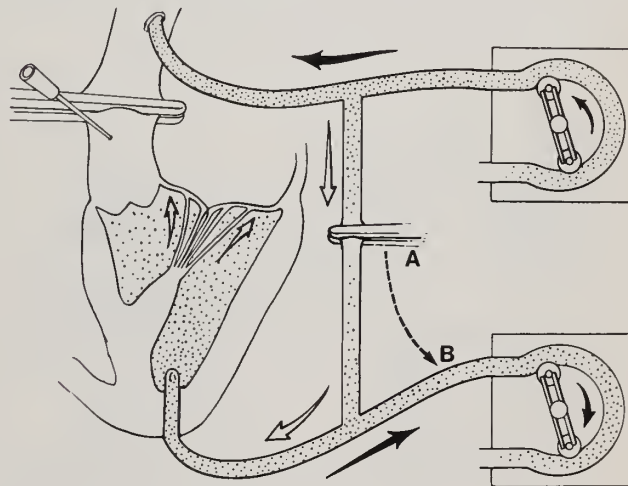


Figure 10. Circuit to test for mitral valve competency. A sidearm of the arterial circuit is connected to the left ventricular apical sump line. By clamping the line between the circuit, blood is removed from the left ventricle. If the clamp is changed from position A to position B (dashed line), arterialized, pressurized blood is now allowed to enter the left ventricle and distend the mitral valve.

Mitral Annular Dilatation

As described, the anterior and posterior trigones serve as a support structure for the mitral annulus. The inter-trigonal distance is the strongest portion of the skeleton of the heart. In pure mitral insufficiency due to annular dilatation, the inter-trigonal distance remains unchanged whereas the remaining mitral annulus dilates (Fig. 11). To correct mitral annular dilatation one must know the intertrigonal distance and apply a ring that will restore the annulus to its normal size. The inter-trigonal distance is easily demonstrated by looping one of the medial

chordae of the anterior mitral leaflet and pulling on it. Two furrows will form that point to the location of the anterior and posterior trigones. Once the trigones are identified and the inter-trigonal distance measured, an appropriate size ring can be selected (Fig. 12).

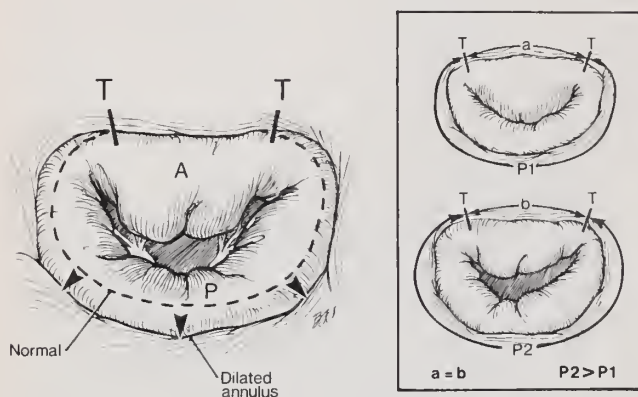


Figure 11. Mitral annular dilatation. By virtue of its relationship to the fibrous trigone, distance T-T, represented as "a" in the figure does not change in conditions of mitral annular dilatation. Consequently, mitral annular dilatation occurs predominantly in the posterior annulus. The right upper panel demonstrates the normal relationship of the annulus to the mitral valve. The bottom panel demonstrates mitral annular dilatation. Since intertrigonal distance remains the same ($a=b$) and there is a dilatation along the posterior annulus (P2), then $P2 > P1$.

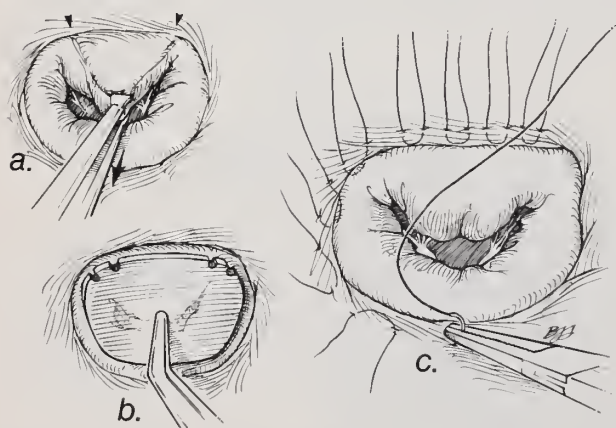


Figure 12. Correction of mitral annular dilatation. a) Traction is placed on the anterior mitral leaflets to demonstrate the location of the trigones (T). b) The appropriate size ring is selected. c) Stitches in the commissure and posterior annular area are placed 4 mm wide and 2 mm wide in the intertrigonal space.

Various devices are available to perform selective annular reduction such as the Carpentier-Edwards,⁶ Duran Flexible-Hancock,⁷ Arcas,²² Puig-Massana-Shiley,²⁴ and Cooley²³ ring. However, we have exclusively used the Duran Flexible Ring for mitral valve annuloplasty during the last eight years.

After an appropriate size ring is selected, mattress stitches are placed in the circumference of the annulus. The stitches in the inter-trigonal space are 2 mm wide, but those in the commissural area and in the free wall along the posterior annulus are 4 mm wide. The stitches are

then placed through the selected ring (Fig. 13). The sutures of the inter-trigonal space are placed in the ring using the same distance relationship as they were placed in the annulus. In the area of the commissures as well as the area along the posterior leaflet, the stitches are placed in the ring closer together.

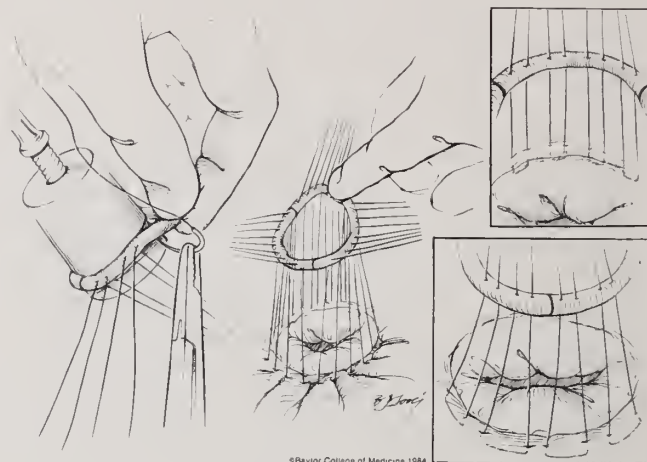


Figure 13. Mitral annular reduction. A ring of the appropriate size has been selected and mounted on the ring holder. The stitches in the inter-trigonal distance are placed through the ring in an equidistant fashion, that is, 2 mm wide. Stitches along the commissures and the posterior annulus which were 4 mm wide are brought through the ring at no more than 1.5 mm apart. The ring is gently lowered into place.

The net result is to "gather up" the annulus to the normal size. There should be 4 or 5 sutures for each third of the selected ring (Fig. 14). After repair is completed, valve competence is tested using the apparatus previously described. Valve competence should be absolute; minor regurgitation is tolerated. An inadequate repair is an indication for immediate valve replacement.

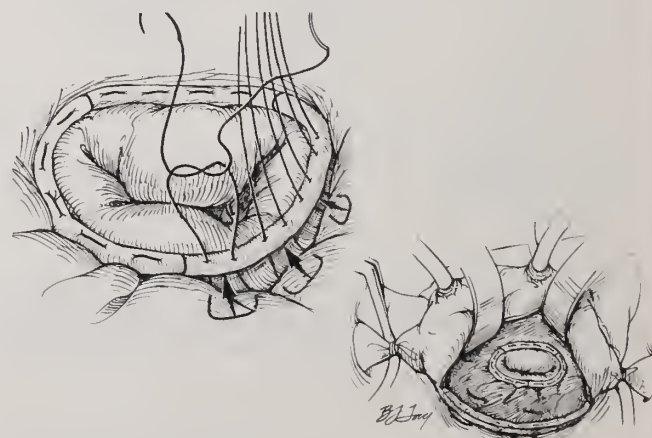


Figure 14. Mitral annular reduction - continued. The ring has been sutured into place. By virtue of the reduction in the width of the stitches as they pass the ring, the posterior annulus is reduced, and advanced toward the anterior mitral leaflet.

Completed annuloplasty. Selective annular reduction and restructuring of the mitral valve to a more normal configuration has been accomplished.

Ruptured Chordae Tendinae

Rupture of marginal chordae tendinae are treated by resection of the chordae and a portion of the leaflet and ring annuloplasty as is illustrated in Figure 15. The ruptured principal chorda is identified by pulling the leaflet with the valvular hook. A segmental resection of the leaflets is performed. The resection of the anterior leaflet is triangular with the apex pointing toward the aortic valve. The resection of the posterior leaflet must be trapezoidal. The valve leaflets are repaired with 6-0 or 5-0 polypropylene sutures. All segmental resections are followed by ring annuloplasty.

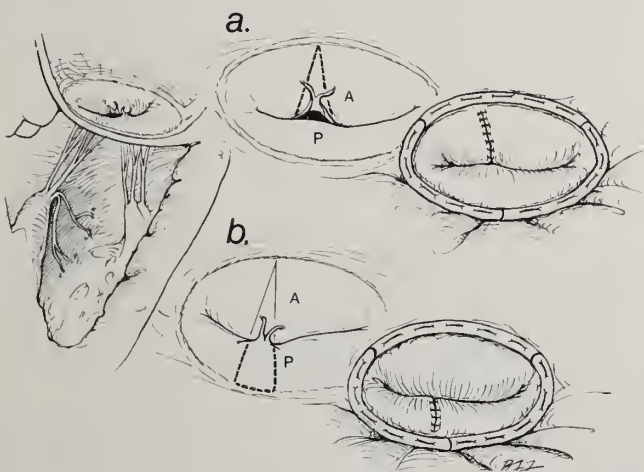


Figure 15. The ruptured chorda is identified by placing traction on the leaflet. For rupture of anterior leaflet chordae (A), a triangular resection of the leaflet is performed with the apex toward the aorta. Rupture of chordae of the posterior leaflet (P) are treated by trapezoidal resection down to the annulus. In both cases the valvular tissue is reapproximated with a continuous suture of 5-0 or 6-0 polypropylene. Annular reduction is utilized in either situation to avoid mitral insufficiency and reduce pressure on the repair.

Chordal Elongation

This is one of the most complex of the valvular repairs. It consists of the plication of the elongated chordae. The amount of chordal elongation is determined by testing the valve under pressure and determining the amount of overlapping of one leaflet over the other. The involved chordae are gathered and pulled with a hook. One must then calculate what constitutes one half of the estimated distance of elongation. The papillary muscle is split, the chordae inserted in a sling and buried inside the papillary muscle with a 5-0 polypropylene suture (Figure 16). The split in the papillary muscle is corrected using a double arm 5-0 polypropylene suture tied over Teflon[®] pledgets (Figure 17).

Competence of the valve must be tested and if mitral insufficiency remains, mitral valve replacement should be carried out. Selective annular reduction without correction of the chordal elongation or resection of the rupture chordae usually does not correct this problem.

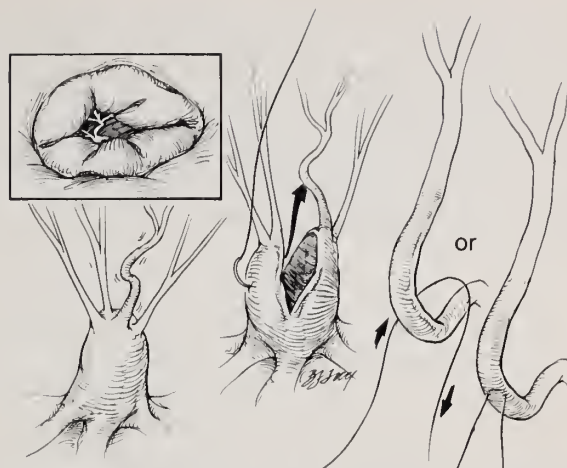


Figure 16. Chordal shortening. Elongated chordae are shortened by burying the excess inside the papillary muscle. The papillary muscle is split as previously described. The slack in the chorda is reduced by the creation of a sling with 5-0 polypropylene suture.

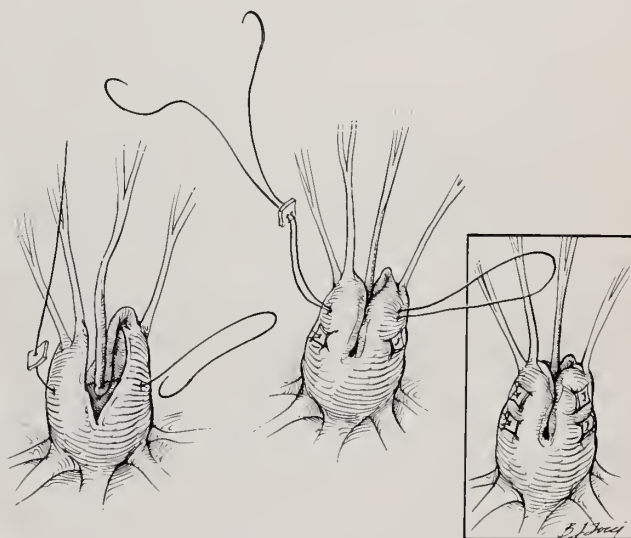


Figure 17. Chordal shortening - continued

The suture can be passed around or through the chorda. Once the shortened chorda is anchored, the papillary muscle is closed with a buttressed 5-0 polypropylene suture.

Leaflet Perforation

Leaflet perforation can result from bacterial endocarditis, and may involve either the anterior or posterior leaflet of the mitral valve. Valve repair should not be attempted in the presence of valve infection.

Valvular leaflet perforations are treated either by partial resection and repair of the gap, using interrupted stitches of 5-0 polypropylene or by debridement of the orifice and insertion of a patch of homologous pericardium. The pericardial patch is anchored with interrupted stitches of 5-0 polypropylene suture.

PATIENT POPULATION

Six-hundred-forty-six patients who underwent mitral conservative surgery at our institutions from May 1974

to September 1982: 301 patients underwent isolated open mitral commissurotomy and 345 patients mitral ring annuloplasty (55 Carpentier and 290 Duran flexible rings). All patients with isolated open mitral commissurotomy or patients with Carpentier rings were excluded from this study. The clinical characteristics of the 290 patients treated with the Duran Flexible ring are summarized in Table II.

TABLE II

Clinical Data Duran Flexible Ring Mitral Annuloplasty		
	Cases	%
Patients	290	
Sex		
Male	61	21
Female	229	79
Ratio	3.7:1	
Age (yr)		
Average	45.8	
Range	14-72	
NYHA Functional Class (Preop)		
Class I	5	1.7
Class II	100	34.4
Class III	152	52.4
Class IV	33	11.5
Diagnosis		
Pure mitral stenosis	80	27.5
Pure mitral insufficiency	51	17.5
Mixed mitral lesions	159	54.8

Most patients operated upon for mitral annuloplasty were preoperatively in New York Heart Association Functional Class II and III (86.8%).

Eighty patients (27.5%) had pure mitral stenosis but a significant mitral insufficiency resulted after commissurotomy, so a Duran flexible ring was required to avoid valve replacement.

The conservative mitral surgical techniques performed in this series included:

- 240 mitral commissurotomies (82.7%)
- 144 papillary muscle splittings (49.6%)
- 39 chordal shortenings (13.4%)
- 22 leaflet repairs (7.5%)
- 290 flexible ring annuloplasties (100%)

Isolated conservative mitral surgery was performed in 144 cases, and concomitant surgery to the aortic or tricuspid valve was performed in the remaining 146 patients.

Mortality

The hospital mortality (less than 28 days) was 3.4% (10 patients). The causes of death were low cardiac output (6), hemorrhage (1), infection (2), and cerebrovascular accident (1).

There were 10 late deaths in this series, which represents a linearized incidence of 0.95% patient-years. The causes of late deaths were thromboembolism (4), cardiac failure (2), death as a result of reoperation (2), cirrhosis of the liver (1), and unknown (1).

Postoperative Evaluation

All surviving patients were evaluated at our institutions, at 3 months, 6 months, and every year postoperatively. Three patients were lost to follow-up. The total duration of follow up was 1,104 patient-years. Ninety-seven percent of patients are NYHA Functional Class I or II postoperatively.

Thirty-four patients who underwent conservative mitral repair sustained a total of 39 thromboembolic episodes, with 4 late deaths. The linearized rate of thromboembolism was 3.6% patient-years.

Fifteen patients required reoperation (5.6%) due to mitral re-stenosis (3), ring dehiscence (8), and unsatisfactory initial surgical results (4). One early and one late mortality followed. The remaining 13 patients are asymptomatic. The actuarial curve of patients free of reoperation is 92.6% at 8 years follow-up.

TRICUSPID VALVE

Indications for Conservative Repair

The indications for conservative surgery on the tricuspid valve are based on the clinical data, hemodynamic study, and surgical findings. The surgical indications cannot be dealt with apart from those of operations for left-sided heart lesions, since they are the determining factor in the postoperative results.

The surgical approach was different if the patients had an organic or a functional lesion. Organic tricuspid disease is thought to be present when the leaflets are thick and distorted with fan chordae usually fused. A functional lesion of the tricuspid valve is thought to be present when annular dilatation is the only pathologic finding. Those patients with grade I organic regurgitation without gradient were ignored. Grade I functional insufficiency was also ignored. Grade II functional insufficiency was either ignored or repaired depending on the arteriolar pulmonary resistances. All patients with grade II organic disease must be operated upon. Grade III organic or functional regurgitation were always repaired (Table III).

TABLE III

Tricuspid Valve		
Indications for conservative repair		
Lesions	Organic	Functional
Grade I	Ignored	Ignored
Grade II	Repair	Depend on APR
Grade III	Repair	Repair

APR = arteriolar pulmonary resistance

Analysis of Tricuspid Valve Anatomy

The tricuspid orifice is the largest of the cardiac orifices. The median circumference in the normal male is 11.4 ± 1.5 cms. From the standpoint of the surgeon this orifice is almost triangular when the heart is in diastole,

with blunted angles corresponding to the commissures.

The tricuspid annulus constitutes the fibrous thickening of the superior border of the right ventricular myocardium. Although it is not as clearly delineated as the mitral annulus, the tricuspid annulus is an integral part of the fibrous skeleton of the heart. This dense connective tissue that separates atrial from ventricular myocardium varies in form and density in the various regions of the tricuspid circumference. The density and demarcation of this tissue varies with sex and age of an individual.¹⁷

The tricuspid valve has three leaflets: the septal, anterior, and posterior. These leaflets have certain indentations and the deepest of these correspond to the commissures which are the antero-septal commissure, the postero-septal commissure and the antero-posterior commissure (Fig. 18).

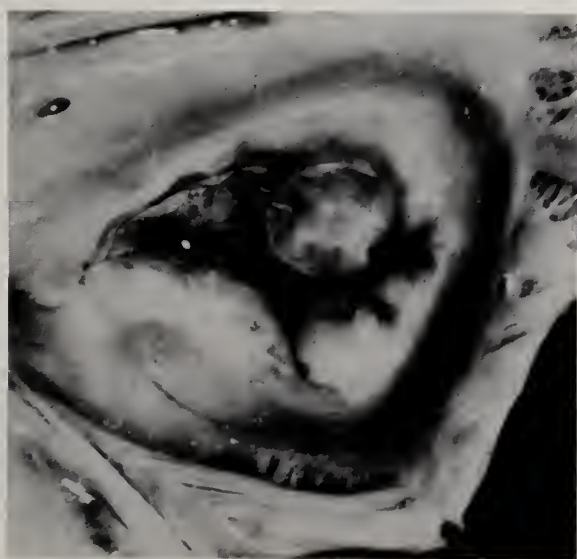
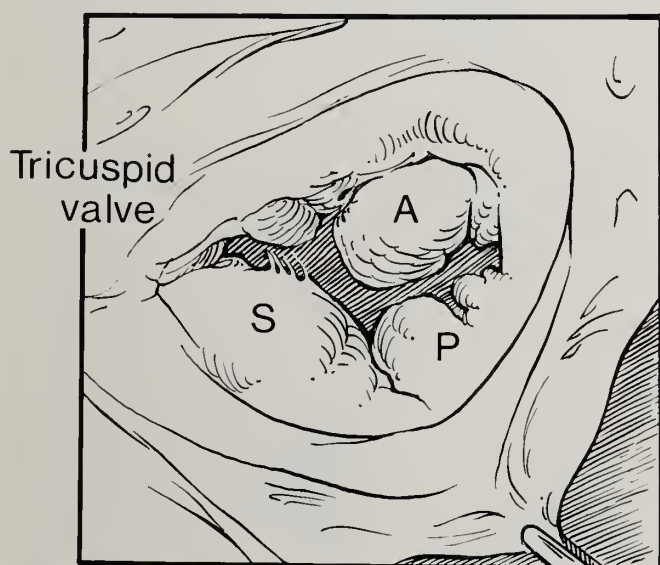


Figure 18. Tricuspid valve. The anterior (A), posterior (P), and septal (S) Numerous indentations are seen in the leaflets and the three deeper ones correspond to the three commissures.

The chordae tendineae of the tricuspid valve can be divided in two large groups: false chordae and true chordae. False chordae are those that interconnect papillary muscles, connect the papillary muscles to the right ventricular wall, or two points between the ventricular wall itself. These are highly variable in number, distribution and dimension. The true chordae are those that originate at the top of the papillary muscle. True chordae occasionally arise in the right ventricular wall as can be seen usually in the chordae that anchor into the septal leaflet. Five types of chordae tendineae are identified in the tricuspid valve: the fan chordae, the rough zone chordae, chordae of the free zone, deep chordae and basal chordae.¹⁷

Fan chordae are very important from the surgical standpoint. The surgeon must know the topography and anatomy of the chordae to be able to carry out a successful commissurotomy. Incorrect section of one of these chordae can result in massive iatrogenic valvular insufficiency which could require tricuspid valve replacement. The chordae of the rough zone, the free border, the deep chordae and the basal chordae are highly variable and not as crucial as the fan chordae for the ultimate results of conservative repair.

The subvalvular apparatus of the tricuspid valve is composed of several papillary muscles; anterior, posterior, and multiple septal papillary muscles. The anterior papillary muscle begins in the antero-lateral aspect of the ventricular wall immediately below the antero-posterior commissure. This papillary muscle fuses with the right prolongation of the septomarginal trabecula and supplies chordae to the anterior and posterior leaflet (Fig. 5). The posterior papillary muscle originates in the inter-ventricular septum under the postero-septal commissure and its chordae tendineae reach the septal and posterior leaflets. Other papillary muscles are multiple and of highly variable distribution with chordae tendineae which are very thin and usually distributed in the septal anterior leaflet (Fig. 19).

The contraction of the right ventricle results in a physiologic narrowing of the tricuspid orifice which favors the apposition of the leaflets permitting competence during ventricular systole. This fact explains that right ventricular dilatation usually result in tricuspid insufficiency due to annular dilatation.

The techniques for tricuspid valve conservative repair are basically:

- COMMISSUROTOMY
- ANNULOPLASTY

Tricuspid Stenosis

Tricuspid repair is usually performed after mitral and/or aortic procedures are performed. A longitudinal right atriotomy is performed with the aorta unclamped (Fig. 20). Atrial retractors are inserted to allow exposure to the tricuspid valve and its annulus. The valve hooks are hinged on the fan chordae and the leaflets are separated. The mirror again aids in the identification of the chordae

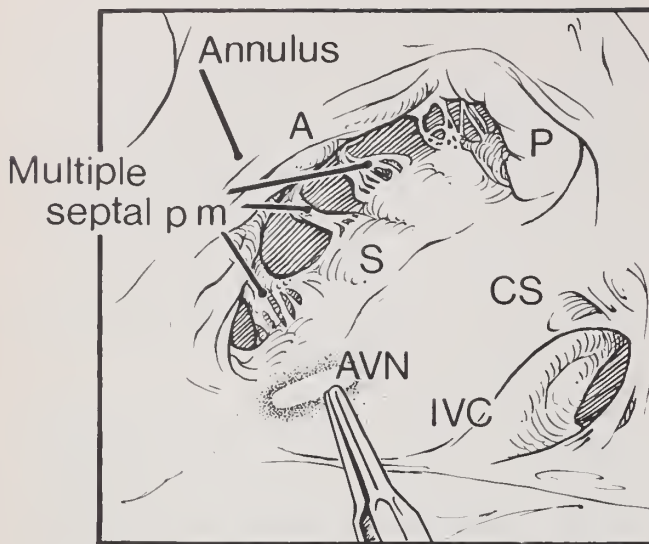


Figure 19. The relationship of the tricuspid valve to other cardiac structures. The orifice of the inferior vena cava (IVC) and the coronary sinus (CS) are noted. The forceps point to the location of the AV node (AVN). Note that there are several septal papillary muscles which send chordae to the edges of the septal leaflet of the tricuspid valve.

and the point of insertion (Figure 20). Commissurotomy is performed between the anterior and septal leaflets if fusion has occurred. It is useful to perform the initial portion of the commissurotomy close to the annulus and then move toward the center of the valve.

It is imperative that the subvalvular mechanism be inspected and that the opening in the tricuspid valve be extended with a hemostat to protect the fan chordae (Fig. 21). If necessary, fused fan shaped chordae can be split but iatrogenic chordal rupture must be avoided. Occasionally it may be necessary to split one of the papillary muscles. The furrow in the papillary muscle is deepened with the blunt end of the knife blade to within 1 cm of the right ventricular wall. Fusion usually occurs between the anterior and septal leaflets (the antero-septal commissure) and occasionally the antero-posterior or postero-septal commissures.

It is important to realize the structures that surround the tricuspid valves when performing conservative repair. Injury to the atrio-ventricular node can result in permanent damage to the conduction system of the heart.

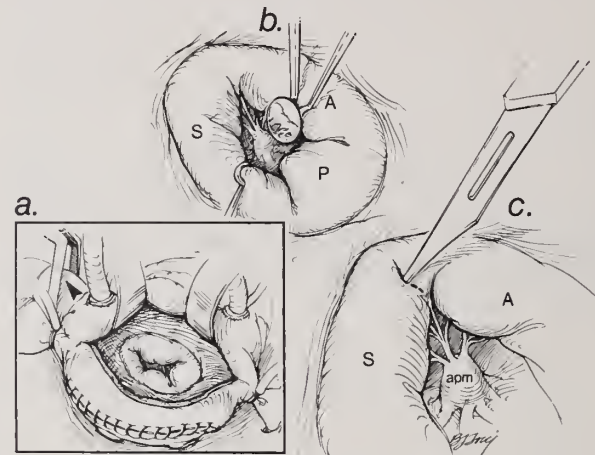


Figure 20. Tricuspid Commissurotomy.

- After the left atrium is closed, the aortic clamp is removed. A longitudinal right atriotomy is made.
- Valvular hooks and mirror are introduced to study the pathology. Fusion usually occurs between the septal and anterior leaflets.
- The valvular fusion is divided with a #11 blade.

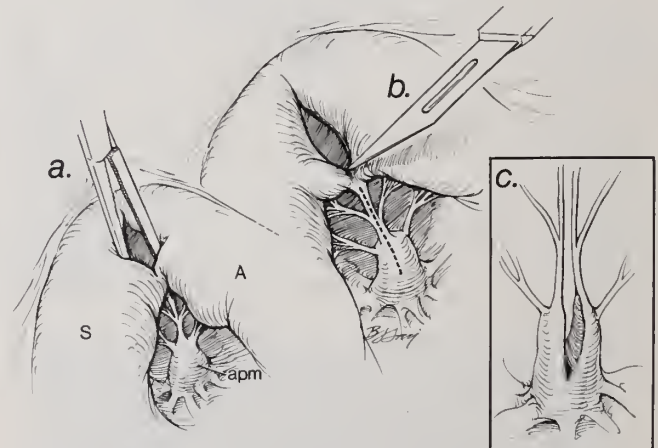


Figure 21. Tricuspid Commissurotomy - (Continued)

- initial incision in the leaflet is spread with a clamp to gently expose the chordal fusion.
- Division of the fused chordae and
- Papillary muscle.

Tricuspid Insufficiency

Dilatation of the tricuspid annulus always occurs along the anterior and posterior leaflets of the tricuspid valve. As in the mitral annulus, that portion of the tricuspid annulus along the septal wall which forms part of the fibrous skeleton of the heart does not dilate. Consequently, the dilatation occurs along the base of the anterior and posterior leaflets of the valve. In normal tricuspid valves, the length of the annulus along the septal portion of the valve is one third of the total circumference of the annulus. This is important when trying to accomplish selective annular reduction (Fig. 22).

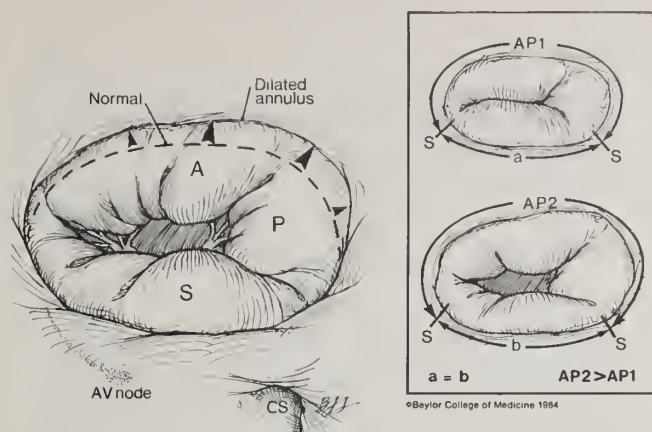


Figure 22. Dilatation of the tricuspid annulus along the anterior (A) and posterior (P) leaflets. The right upper panel demonstrates the normal relationship of the right annulus. The right bottom panel shows tricuspid annular dilatation. Since the distance "SS" remains the same ($a=b$), and there is dilatation along the anterior and posterior annulus ($AP2$), then $AP2 > AP1$.

Tricuspid annuloplasty can be accomplished with the use of several techniques: DeVega or prosthetic annuloplasty (Carpentier,⁶ Duran,⁷ Cooley,²³ Arcas,²² Puig-Massana).²⁴

As previously mentioned, we only utilize the Duran Flexible Ring tricuspid annuloplasty technique.

The measurement of the length of the septal portion of the annulus is determined. As can be seen in Figure 23, stitches of 2-0 Ethibond ^R are placed at the base of the septal leaflet, approximately 2 mm wide. Once these stitches are placed, the length of the septal portion of the annulus is measured and the appropriately sized ring is selected. Stitches are then placed along the anterior and posterior aspects of the annulus approximately 4 mm wide. These stitches are then placed through the appropriate ring and they should be no further apart than 1.5 mm as they emerge from the ring. As the stitches are placed on the ring those in the septal portion maintain the same relationship to the ring as they did in the annulus. Those along the anterior and septal portions are placed close together and gathered. In this manner one accomplishes selective annular reduction along the anterior and posterior segment of the annulus (Fig. 24).

Once the repair has been accomplished, the adequacy of the repair must be tested. The apparatus previously used to decompress the left ventricle and test mitral valve repair is then introduced into the right ventricle in a retrograde manner via a stab wound in the pulmonary artery. The right ventricle is then distended with blood under pressure and the adequacy of repair ascertained.¹⁸ If a satisfactory competence is not restored the repair must be revised or the tricuspid valve replaced.

PATIENT POPULATION

From January 1975 to January 1982, 468 tricuspid annuloplasties were performed at our Institutions (31 Carpentier rings, 34 De Vega procedures, and 403 Duran flexible rings), and 170 tricuspid commissurotomies.

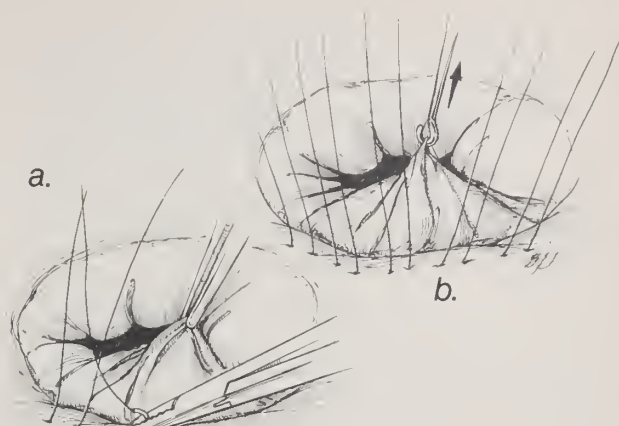


Figure 23. Tricuspid Annuloplasty Ring.

a., b. 2 mm wide stitches of 2-0 Ethibond ^R are placed at the base of the septal leaflet. These stitches are placed superficially, with traction on the leaflet to avoid injury to the A-V Node. Once the stitches along the septal leaflet are placed, the size of the required ring is determined using the same method as for the mitral valve. The stitches along the posterior and anterior leaflets are 4 mm wider and deeper into the annulus.

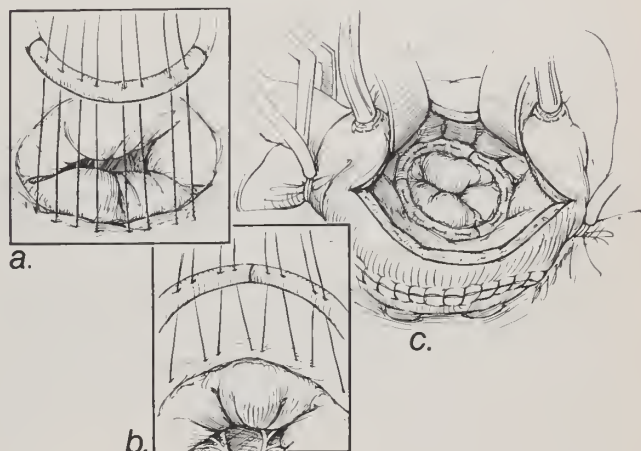


Figure 24. Tricuspid Annuloplasty Ring.

A. The stitches along the septal leaflet are placed through the ring equidistant to their placement in the annulus.

B. Stitches along the posterior and anterior portion of the annulus (4 mm wide) are placed through the ring about 1.5-2.0 mm wide. Annular reduction and remodeling are achieved in this manner.

C. Completed annuloplasty

The clinical characteristics of 403 patients with Duran ring tricuspid annuloplasty are summarized in Table IV. Most patients were preoperatively in NYHA Functional Class III-IV (85%). The cardiothoracic index was more than 0.60 in 75% of patients. An associated mitral valve procedure was performed in 268 (66.5%) patients and mitral and aortic procedures was done in 135 cases (33.5%).

The diagnosis was organic tricuspid disease in 198 patients and functional disease in 205. Four patients with congenital tricuspid disease were excluded from this study.

All patients had a full hemodynamic study before surgery, with bi-ventriculography. Tricuspid stenosis or insufficiency were defined angiographically as previously reported (20, 21).

TABLE IV

Clinical Data		
Duran Flexible Ring Tricuspid Annuloplasty		
	Cases	%
Patients	403	
Sex		
Male	108	26.7
Female	295	73.3
Ratio	2.7:1	
Age (yr)		
Average	49.3	
Range	14-77	
NYHA Functional Class		
Class I	3	0.7
Class II	65	16.2
Class III	234	58.0
Class IV	101	25.1
Cardiothoracic Index		
50%	16	3.9
50-70%	289	71.8
70%	98	24.3
Preoperative Diagnosis		
Mitral and tricuspid disease	268	66.5
Mitral, aortic, and tricuspid disease	135	33.5
Pathology		
Organic tricuspid disease	198	49.2
Functional tricuspid disease	205	50.8

Mortality

The overall hospital mortality was 9.6% (39 cases). The causes of death were low cardiac output (11), infection (9), hemorrhage (8), arrhythmias (6), and other causes (5).

There were 22 late deaths in this series (6.2%). Six patients died during reoperation. Other causes of death were: sudden death (4), cardiac failure (4), infective endocarditis (2), thromboembolism (2), pulmonary embolism (1), hemorrhage (1), malignancy (1), and of unknown origin (1).

Postoperative Evaluation

As in the mitral group, all surviving patients were evaluated at our institution at 3 months, 6 months, and every year postoperatively. Seven patients were lost to follow-up. The total duration of follow-up was 1401.3 patient-years. The average follow-up interval for surviving patients was 51.3 months with a range of 1 year to 8 years.

Ninety-six percent of patients are in NYHA Functional Class I or II after surgery, 12 cases in Class III, and 2 in Class IV. Postoperative Functional Class of this group of patients was related to the quality of the left-sided repair, regardless of whether the tricuspid valve had been correctly or incorrectly repaired.

Permanent atrioventricular block developed after surgery in 9 patients (2.2%), all requiring a permanent pacemaker.

Thirteen patients (3.2%) were reoperated for ring dehiscence (9), residual tricuspid insufficiency without dehiscence (3), and leaflet defect (1). Those patients were reoperated 2 to 88 months after tricuspid annuloplasty. In all cases, the indication for reoperation was related to the left heart lesion. Seven patients died and 6 survived the reoperation.

CONCLUSIONS

Mitral Valve:

- * Reconstructive surgery of the mitral valve can be successfully performed in almost 50% of patients with mitral valve disease.
- * Adequate exposure of left atrium and mitral valve (leaflets and subvalvular apparatus) is the key surgical step for conservative repair.
- * The reproducibility of the reconstructive mitral techniques depends upon the experience and disposition of the surgical group.
- * Reconstructive valvular surgery is less expensive and avoids prosthetic valve-related complications.
- * In our experience, the reconstructive mitral surgery has shown better long-term results than valve replacement.

Tricuspid Valve:

- * A complete preoperative right and left heart hemodynamic study with bi-ventriculography is mandatory to perform tricuspid reconstructive surgery.
- * Preoperative pulmonary resistance and the quality of the left-side lesion repair^{25,26} are the determining factors in the postoperative results of these patients.
- * A significant number of patients with organic tricuspid lesion (49%) shows the importance of a careful preoperative hemodynamic study and preoperative search for them.
- * Precise knowledge of the normal and abnormal tricuspid valve (annulus, leaflets, commissures, subvalvular apparatus and surrounding structures) is also mandatory to avoid iatrogenic complications (ex. AV block, residual tricuspid stenosis).
- * Tricuspid surgery is preferably performed using non-ischemic conditions.
- * The reconstructive tricuspid surgery with Duran Flexible Ring has demonstrated, in our experience, very satisfactory long-term follow up with minimal postoperative complications.

Resumen: Los enfermos sometidos a reemplazos valvulares demuestran serios problemas si son seguidos por largo tiempo. Dichos enfermos sufren embolias sistémicas o fallo de las válvulas en un alto porcentaje de los casos. Los resultados desalentadores observados han creado un renacimiento en América de las técnicas de reparo de las válvulas atrio ventriculares utilizadas extensamente por cirujanos europeos.

En este trabajo revisamos la anatomía, patología, técnicas de reparo y resultados de cirugía conservadora de las válvulas atrioventriculares. En 693 enfermos se utilizó el anillo flexible de Duran y fueron seguidos por un período mínimo de ocho años. De los 290 pacientes que fueron sometidos a reparación mitral, 10 pacientes (3.4%) fallecieron durante el primer mes. Durante el período de ocho años de seguimiento otros diez pacientes (3.4%) fallecieron; cuatro de tromboembolismo, dos de fallo cardíaco, dos durante una reoperación, uno de cirrosis del hígado y uno de causa no conocida.

De los 403 enfermos sometidos a reparo tricuspideo, treinta y nueve fallecieron durante el primer mes (9.6%). Durante el período de seguimiento de ocho años, otros veintidos pacientes (6.2%) fallecieron de causas diversas.

Concluimos que los resultados de la cirugía conservadora es superior a la de reemplazo valvular y que en todo caso de enfermedad mitro-tricuspidea se debe hacer un esfuerzo por reparar la válvula afectada.

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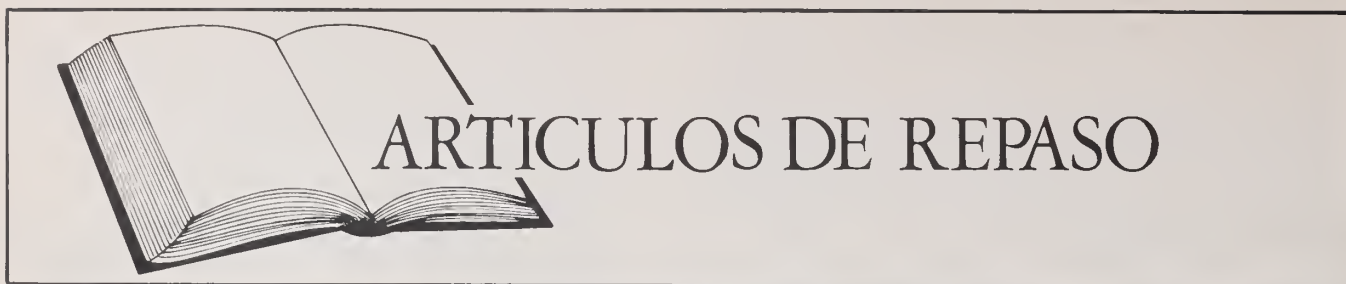
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Bilirubinemias Congénitas

Miguel S. Pastrana, M.D.

Los adelantos recientes en el metabolismo de la bilirubina y sus derivados han servido de base para entender más a fondo los defectos metabólicos que conocemos como bilirubinemias congénitas. Es el propósito de este resumen describir de una forma sencilla estas condiciones y sus defectos, y a la vez intentar dar una idea del manejo del paciente que se presenta solamente con hiperbilirubinemia.

La bilirubina es el producto final del catabolismo de "HEME" que de por sí es parte esencial de las moléculas de hemoglobina, mioglobina y otras hemoproteínas como el citocroma P.450, las catalasas y peroxidasas que se encuentran en el hígado. La elevación en sangre de este pigmento causa que éste se deposite en distintos tejidos como piel, ojo, etc. produciendo el cuadro que reconocemos como ictericia. Dependiendo de la fase de conjugación de este pigmento en el hígado la elevación puede deberse a bilirubina conjugada o no conjugada o según describe en la prueba de laboratorio de Van den Bergh, bilirubina indirecta (no conjugada) o bilirubina directa (conjugada). Esta diferencia en el estado de conjugación da base para la clasificación de las hiperbilirubinemias.

Metabolismo de Bilirubina

La bilirubina se forma del metabolismo de las moléculas que contienen un componente llamado "Heme". Este está compuesto por unos anillos de piroles unidos, que al ser abiertos en el llamado puente alfa se forma biliverdina IX, (reductasa de biliverdina) la cual es reducida químicamente a bilirubina IX. Esta molécula es no polar e insoluble en agua y depende para su transporte en sangre de unirse a la albúmina. El "Heme" puede tener su origen en la hemoglobina que se obtiene luego de la destrucción de células rojas (85%) o del metabolismo de moléculas no relacionadas a eritrocitos como mioglobina, etc.

El transporte de bilirubina no conjugada en plasma con albúmina es potencialmente saturable dependiendo del nivel de bilirubina no conjugada o de la utilización de albúmina en el transporte de otras moléculas. Esto es muy importante en recién nacidos si se utilizan drogas que compitan con la bilirubina para su transporte (salicilatos, sulfas, etc.) La bilirubina no conjugada no transportada en albúmina se difunde a tejidos y es espe-

cialmente tóxica al cerebro (kernícteros). Ya que no es soluble en agua, el modo de excreción de bilirubina tiene que ser a través del hígado donde se combina o conjugada con otra molécula que la haga más polar. Esta fase de captación por el hígado, conjugación y excreción del producto conjugado en los canalículos es muy compleja y los adelantos enzimáticos han sido enormes.

La bilirubina no conjugada llega al hígado por dos vías: la sangre, y el sistema linfático. Posiblemente en receptores en la membrana del hepatocito se disocia la albúmina de la bilirubina y esta entra al hepatocito donde unas proteínas llamadas "ligandinas" (Y y Z) transportan la bilirubina hasta el lugar de conjugación. Estas proteínas también transportan esteroides, bromosulfotaleína (BSP) y agentes usados para visualizar las vías biliares. La conjugación de la bilirubina ocurre en las microsomas del retículo endoplásmico liso ("smooth endoplasmic reticulum"). Se conjugada a través de la enzima glucuronil transferasa, el cual transfiere una molécula de ácido glucurónico y la conjugada con bilirubina formando bilirubina monoglucurónica. Existe controversia con relación a la manera en que se le añade a esta molécula otro ácido glucurónico, pero se sabe que el mayor componente de bilirubina conjugada es el diglucurónico. En adición a la bilirubina, muchas sustancias son conjugadas por el hígado con ácido glucurónico y esto también es una fase competitiva metabólicamente. También sabemos que la enzima glucuronil transferasa se encuentra en poca cantidad en el feto y aumenta hasta niveles de adulto alrededor de dos semanas luego de nacido el niño. También sabemos que esta enzima es "inducible" por distintas sustancias químicas como lo son otras enzimas en el hígado (citocromas P450).

La fase de excreción de la bilirubina conjugada en el canalículo biliar es un proceso que envuelve gasto de energía. Este proceso también es saturable y es posiblemente el paso que limita la excreción de bilirubina en animales normales excepto cuando hay defectos congénitos en las enzimas de conjugación. A nivel del canalículo hay dos procesos distintos de excreción para sales biliares y bilirubina y existen defectos metabólicos en la excreción de bilirubina en el canalículo en algunos pacientes. Estos también envuelven la excreción de BSP y otros pigmentos,

pero no de sales biliares. (Ej. Síndrome de Dubin Johnson)

Luego de la molécula llegar al intestino por la bilis, parte, mayormente de la bilirubina monoglucurónica, se absorbe y entra al conocido ciclo entero hepático. El resto se degrada por bacterias a otros pigmentos y se excretan o reabsorben, pero son solubles en agua y se pueden excretar en la orina.

Defectos congénitos en el metabolismo de bilirubina

A-Bilirubinemias No Conjugadas. Estas son elevaciones producidas por cualquier defecto que aumente la producción de bilirubina: hemólisis (en personas normales, el hígado tiene una capacidad extraordinaria para aumentar su metabolismo y evitar aumentos en bilirubina significativos), defectos de captación, defectos de transporte en el hepatocito o deficiencias enzimáticas en los enzimas de conjugación.

1- Bilirubinemia no conjugada del recién nacido. Al nacer, el niño no tiene sus sistemas totalmente desarrollados para metabolizar la bilirubina. Si a esto se le añade un problema de hemólisis, niveles más bajos de albúminas, factores metabólicos (acidosis, anoxia) o drogas que compitan con bilirubina para su transporte con albúmina, tendremos elevaciones en la bilirubina indirecta que potencialmente, dependiendo de los problemas adicionales mencionados, pueden llegar a niveles peligrosos de saturación de albúmina y depósito en los tejidos cerebrales. Usualmente, si no hay complicaciones, esta elevación es fisiológica y persiste menos de una semana y rara vez los niveles de bilirubina subrepasan los 12-15 mg. %. Se puede pensar en casos no fisiológicos y si patológicos si ocurren los siguientes:

- ictericia en las primeras 36 horas de nacido.
- ictericia sobre 12 mg. %
- persistencia de la ictericia sobre 8 días.
- niveles de bilirubina conjugada sobre 1.5 mg. %

Distintas modalidades de tratamiento han sido usadas en los casos más severos: fototerapia, fenobarbital, albúmina intravenosa y exsanguíneo-transfusión. Con la intención de discutir sólo algunas de estas modalidades y debido a su exceso de uso, discutiremos el tratamiento de fototerapia.

Desde 1958 se han publicado múltiples trabajos sobre el uso y eficacia de la fototerapia. Luz de alrededor de 400 NM transforman la molécula de bilirubina a pigmentos incoloros por foto oxidación de la bilirubina depositada en la piel. Estos pigmentos no necesitan ser conjugados para su excreción. Se debe limitar el uso de la foto terapia a solamente niños prematuros con niveles de bilirubina sobre los 8-10 mgs. y solo en niños a término con problemas potenciales de hiperbilirubinemias severas ya que esta modalidad de tratamiento tiene potenciales efectos nocivos.

2- Bilirubinemia producida por la leche materna. Se han descrito casos de hiperbilirubinemias indirectas prolongadas en niños que consumen leche materna. Comienza la ictericia alrededor del 5to. día de nacido y persiste mientras se continúe la lactación. La causa de este problema es probablemente una sustancia en la leche

materna (pregnane-3-alfa-20 beta-diol) que inhibe la conjugación. Otros investigadores creen que la sustancia inhibidora es un ácido graso o lipoproteína en la leche materna de algunas personas.

3- Síndrome de Crigler-Najjar o Arias I. Esta condición demuestra una deficiencia total del enzima de conjugación e incapacidad de inducir su producción con fenobarbital. Es una condición heredada por genes autosómicos recesivos. Ocurre temprano en el recién nacido con aumento de la bilirubina no conjugada sobre 20 mg., el desarrollo de kerníctero y muerte temprana. El diagnóstico se debe sospechar en pacientes con historial familiar de hiperbilirubinemia y se comprueba con niveles de glucuronil transferasa en especímenes obtenidos por biopsias de hígado. No hay tratamiento específico a pesar de que se ha conseguido prolongar la vida en algunos pacientes a través de la combinación de intercambios de sangre y fototerapia intensiva.

4- Crigler-Najjar o Arias II. La deficiencia en estos pacientes es total del enzima pero se puede inducir su producción a través del uso de fenobarbital. Se hereda como dominante autosómico, se diferencia del tipo I por: su respuesta a fenobarbital, elevación más lenta de la bilirubina, color normal de la excreta y prolongación de la vida hasta adolescencia en muchos casos. Los casos más leves de esta condición se pueden confundir con el síndrome de Gilbert.

5- Hiperbilirubinemia Familiar no Conjugada (Síndrome de Gilbert). Esta condición sumamente común (alrededor de 6-10 % de la población americana) es una condición benigna descrita como elevación leve de la bilirubina indirecta en ausencia de evidencia de hemólisis, a pesar de que un cuadro hemolítico puede desenmascarar este problema. Muchos casos descritos se presentan asociados a cuadros de hemólisis crónica. Su único síntoma es ictericia que se puede confundir al hacerse obvia en un cuadro viral no específico. Las pruebas hepáticas son totalmente normales incluyendo niveles de sales biliares y gamma glutamil transpeptidasa. Esta es una condición familiar con cierta preferencia por los varones. El problema metabólico no está claro y puede ser por una o varias alteraciones: en la captación de bilirubina por el hepatocito, transporte deficiente en el citoplasma por deficiencia de ligandinas y/o deficiencias parciales de la glucuronil transferasa. La excreción de otros pigmentos como BSP y de sales biliares es usualmente normal.

Se han diseñado ciertas pruebas para la confirmación del síndrome de Gilbert y usualmente las más útiles son la de privación calórica o ayuna y la otra, menos usada, es la prueba de ácido nicotínico. Ninguna es específica para esta condición. Se sabe que la ayuna es un estímulo para la oxigenasa de heme, paso esencial para la producción de bilirubina. Al ayunar, especialmente si hay deficiencia calórica, se estimula la producción de esta enzima, aumentando la carga de bilirubina indirecta al hígado y en casos de Gilbert, aumentando ésta en plasma. El uso de drogas inductoras de glucuronil transferasa, como fenobarbital, disminuye la bilirubina en casos de Gilbert, pero por lo leve de esta elevación en estos casos, no se justifica su uso. Los corticosteroides aumentan la captación de bilirubina por el hepatocito y esto pudiera explicar este efecto cuando se usa en pacientes ictericos.

La biopsia hepática no está indicada en casos de Gilbert y fuera de un aumento en la lipofuscina no específica ni aún la microscopia electrónica detecta defecto morfológico alguno.

B-Bilirubinemias Conjugadas

Tres defectos de excreción de bilirubina conjugada han sido descritos: Dubin-Johnson, Rotor y Colestasis benigna recurrente.

1- Síndrome de Dubin-Johnson- En 1954, Dubin y Johnson describieron varias familias, incluyendo una de puertorriqueños, con elevación de bilirubina conjugada sin hemólisis. El hígado de estos pacientes presentaba una coloración casi negra y en las biopsias se demostraba una pigmentación de gránulos grandes, intra hepatocíticos especialmente en las áreas alrededor de las venas centrales de los lobulillos. Se han descrito alrededor del mundo estos casos sin preferencia sexual y con un patrón recesivo hereditario.

Estos pacientes se presentan con hiperbilirubinemia directa, los síntomas pueden variar con astenia, etc., y el examen físico es totalmente negativo excepto por la ictericia. No aquejan prurito, ya que el metabolismo de las sales biliares es normal, pero el grado de ictericia puede aumentar de los niveles usuales de 2-5mg.% cuando se usan drogas como contraceptivos orales. Las pruebas de laboratorio enzimáticas son normales, pero el diagnóstico se puede confirmar por tres hallazgos adicionales que son: una curva típica de elevación tardía de BSP, no visualización de la vesícula en colecistogramas y un patrón característico en el HIDA scan para las vías biliares. Como se dijo anteriormente, los niveles de sales biliares son normales a pesar de reportes de alteración de excreción de "ursodeoxycholate". En 1967, Koskelo reportó un patrón característico de excreción de coproporfirina I en la orina de pacientes con Dubin-Johnson, en el cual el porcentaje de coproporfirina I es mayor que el porcentaje en pacientes normales (80%).

2- Síndrome de Rotor- Descrito en 1948; se pensó que esto era un variante de Dubin-Johnson pero al presente se consideran dos condiciones distintas. No se sabe su modo de herencia y se diferencia de Dubin-Johnson en que el hígado es de apariencia normal, macro y microscópicamente, la curva de BSP normal, hay visualización normal de la vesícula y elevación de coproporfirinas totales en la orina a pesar de también demostrar elevación de la coproporfirina I.

3- Colestásis Intra-hepática Benigna Recurrente. Descrita en 1959; se caracteriza por episodios recurrentes de colestasis con elevación de bilirubina y sales biliares asociadas a ictericia y prurito. Los episodios de colestasis duran varias semanas pero en algunos casos han durado años.

Manejo del Paciente con Ictericia Sin Ninguna Otra Alteración.

Vemos frecuentemente pacientes con elevación en la bilirubina descubiertos en pruebas de laboratorios hechas rutinariamente o en pacientes con ictericia que no presentan otras anomalías en sus pruebas de laboratorio. Luego de un examen físico y un buen

historial, especialmente un historial familiar completo, le ordenamos a estos pacientes fraccionamiento de su bilirubina para diferenciar entre las hiperbilirubinemia directa (conjugada) y la indirecta o no conjugada. La mayor parte de estos pacientes se presentan sin síntomas, pero algunos han sido diagnosticados incorrectamente como casos de Hepatitis Viral al notarse su ictericia en cuadros virales no específicos. Las pruebas básicas hepatológicas nos ayudan a excluir enfermedad significativa en el hígado. Estas pruebas son gamma glutamil transpeptidasa, electroforesis de proteína y antígenos y anticuerpos a los virus hepatotrópicos.

A los pacientes con hiperbilirubinemia indirecta les hacemos pruebas sanguíneas para excluir cuadros hemolíticos crónicos, estas pruebas son: patrón de hemoglobina, Coombs directo e indirecto y conteo de reticulocitos. También le hacemos niveles de sales biliares en ayunas y post prandiales. Si todas estas pruebas confirman solo un defecto en el metabolismo de la bilirubina de las antes mencionadas, el tratamiento variará de acuerdo a la severidad de la condición. En los casos de Gilbert y en neonatos el manejo es usualmente conservador. En los casos de Arias tipo II se le induce su sistema metabólico usualmente con fenobarbital como antes mencionamos. Los casos de Arias Tipo I se manejan con fototerapia e intercambio de sangre y aún así su pronóstico es pobre. Recientemente se ha desarrollado un bloqueador de "hem-oxigenasa" que disminuye el paso metabólico esencial para la producción de bilirubina y de esta manera evita su elevación.

En casos de hiperbilirubinemia conjugadas en adición a los niveles de sales biliares hacemos un sonograma de las vías biliares, una curva de BSP y el patrón de excreción de coproporfirinas en la orina. Esta información en adición a estudios radiográficos de la vesícula nos ayuda al diagnóstico diferencial en estos casos. La biopsia de hígado esta indicada solo en casos que exista alguna duda sobre el diagnóstico por el especialista o en casos de investigación clínica.

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As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions: *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness*, headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation, see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness; lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under "Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "Causal Relationship Unknown" if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

MED B-7S

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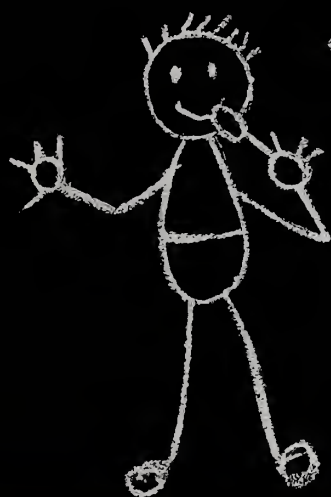
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Please see following page for brief summary of prescribing information.

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Indications and Usage: 'Rynatan' is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications: 'Rynatan' is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings: Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine oxidase (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions: *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for Patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery, while using this product.

Drug Interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed with 'Rynatan'.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with 'Rynatan'. It is also not known whether 'Rynatan' can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 'Rynatan' should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 'Rynatan' should not be administered to a nursing woman.

Adverse Reactions: Adverse effects associated with 'Rynatan' at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Note: The following sections are optional and may be omitted.

Overdosage: *Signs & Symptoms*—may vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment—Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration: Administer the recommended dose every 12 hours.

'Rynatan' Tablets. Adults—1 or 2 tablets.

'Rynatan' Pediatric Suspension: Children over six years of age—5 to 10 ml (1 to 2 teaspoonfuls); Children two to six years of age—2.5 to 5 ml (½ to 1 teaspoonful); Children under two years of age—Titrate dose individually.

How Supplied

'Rynatan' Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and bottles of 500 (NDC 0037-0713-96).

'Rynatan' Pediatric Suspension: dark-pink with strawberry-currant flavor, in pint bottles (NDC-0037-0715-68).

Storage: 'Rynatan' Tablets—Store at room temperature; avoid excessive heat—(above 40°C/104°F).

'Rynatan' Pediatric Suspension—Store at controlled room temperature—between 15°C–30°C (59°F–86°F); protect from freezing. Issued 1/82



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Breast cancer found early and treated promptly has an excellent chance for cure. About a week after your period, practice this self-examination.



1. In bath or shower.

Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.





MEDICAL ASPECTS OF NUTRITION

Alcohol-Nutrition Interaction*

Charles S. Lieber, M.D.**

Alcohol is both a food and a drug. Alcohol is rich in energy but it is consumed for its mood-altering effects. It is a psychoactive drug which exerts various toxic side effects. Tissues most strikingly affected by alcohol are the liver and the brain.¹

Several neurological complications of alcoholism, such as polyneuropathy and Wernicke's syndrome, once ascribed to a direct toxic effect of alcohol, are now recognized as vitamin deficiencies resulting primarily from an inadequate thiamin intake. A reverse trend of thought has occurred with regard to liver disease. Whereas traditionally, the disorders affecting the liver have been attributed exclusively to nutritional deficiencies accompanying alcoholism, studies carried out over the last two decades indicate that alcohol per se can be incriminated as a toxic etiological factor.¹

In addition, secondary malnutrition has now come to the forefront with the demonstration that alcohol has also some direct effects upon the gastrointestinal tract, resulting in maldigestion and malabsorption of nutrients.¹ Recent studies in this area of alcohol/nutrition interactions will be summarized here. However, in order not to exceed the scope of this review, some areas will not be discussed. They include the alcohol-zinc interaction and the important relationship between alcohol and lipoprotein (including high density lipoprotein) abnormalities; these areas have been the subject of recent comprehensive reviews.^{1, 2, 3}

Ethanol-Vitamin Interactions

Vitamin supplementation is commonly practiced in the treatment of alcoholism, whether deficiencies are present or not. Such an approach to therapy may be harmless, as in the case of some water-soluble vitamins such as thiamin. The administration of excess thiamin can be justified on the ground that when given in large amounts, passive absorption can overcome deficiencies resulting

from decreased active absorption of thiamin at low concentrations.⁴

Another water-soluble vitamin commonly lacking in the alcoholic is folic acid.⁵ In addition to decreased intake and malabsorption, it has been recently demonstrated that there is increased urinary excretion of folic acid after alcohol ingestion.⁶

Not all water-soluble vitamins, however, are harmless when used in excess. Pyridoxine toxicity has been recently described.⁷ Therapeutic use of lipid-soluble vitamins (such as vitamin A) is also complicated in view of their intrinsic toxicity. Vitamin A depletion in the alcoholic must be considered seriously, since deficiencies are common. Indeed, it has long been recognized that alcoholics with cirrhosis have night blindness (which is possibly related to vitamin A deficiency), decreased plasma vitamin A, as well as retinol-binding protein (RBP) levels. These complications have usually been attributed to malnutrition. It is also possible that part of these complications may result from hepatic injury, because decreased plasma vitamin A and RBP levels have been reported in patients with liver disease without apparent alcohol intake. Furthermore, information has recently become available concerning direct effects of alcohol on vitamin A metabolism. It is now realized that alcoholics, even at the early stages of liver involvement, may have extremely low levels of vitamin A in their livers despite normal circulating vitamin A and the absence of obvious vitamin A malnutrition.⁸ The very low hepatic vitamin A levels might be responsible for some structural or functional abnormalities including abnormal lysosomes.⁹ Therefore, indication for vitamin A supplementation in the alcoholic may be expanded to possible correction of liver dysfunction.

Vitamin A therapy, however, is complicated by its potential hepatotoxicity which was found to be enhanced after chronic alcohol consumption.^{10, 11} Thus, the "therapeutic window" for vitamin A in the alcoholic is relatively narrow.

Abnormalities of Amino Acids and Their Implications for Therapy

Plasma amino acid abnormalities are common in alcoholics. Dietary protein deficiency depresses branched-

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**Section of Liver Disease & Nutrition Alcohol Research & Treatment Center Veterans Administration, Treatment Center, Bronx, New York 10468, and Mount Sinai School of Medicine, New York, New York 10029

chain amino acids and alpha-amino-n-butyric acid (AANB). By contrast, chronic alcoholic consumption selectively increased these amino acids. Moderate liver injury had no significant effects on these amino acids, whereas advanced cirrhosis depressed branched-chain amino acids. Thus, plasma branched-chain amino acids and AANB in the alcoholic are affected by at least three variables: dietary protein deficiency and advanced cirrhosis, which tends to decrease these amino acids, and chronic alcohol consumption, which tends to increase them.¹² An attempt has been made to incorporate AANB with other measurements as a marker of heavy drinking. When used sequentially, it is helpful, in combination with gamma glutamyl transpeptidase, to detect relapse after treatment.¹³ However, because of interference by other factors that affect amino acids, AANB, when used by itself, was found to be wanting both in sensitivity and specificity.

The observation that patients with PSE (portal-systemic encephalopathy) often have low branched-chain amino acids but elevated aromatic amino acids in their plasma, generated the hypothesis that this amino acid imbalance could promote PSE. Attempts were made at correcting the imbalance by administering an amino acid mixture (F080: HepatAmine) enriched with branched-chain amino acids (valine, leucine, isoleucine) but containing decreased amounts of aromatic amino acids (phenylalanine, tyrosine, tryptophan).¹⁴ It was found in a multicenter randomized trial that branched chain amino acid administration reduced the concentrations of aromatic amino acids.¹⁵ This neither improved cerebral function nor decreased mortality in patients with hepatic encephalopathy.¹⁵ It was also found that plasma amino acids did not change with improvement in PSE and that abnormalities of plasma amino acids did not prevent maintenance or attainment of positive nitrogen balance in patients with acute alcoholic hepatitis.¹⁶

Similar equivocal results were obtained in attempts at manipulating amino acids through altering dietary protein. It is, of course, well known that a decrease in dietary protein in patients with severe liver disease intolerant to nitrogenous load will improve PSE. In addition, vegetable-derived protein has been claimed to be superior to animal protein. Shaw, et al., found no advantage, however, in switching from animal to vegetable protein in terms of encephalopathy or nitrogen balance.¹⁷ A similar dietary regimen was not associated with a change in the neurological impairment.¹⁸ Negative results were also obtained with Hepatic-Acid, an enteral amino acid formula containing reduced levels of aromatic and increased levels of branched-chain amino acids.¹⁹

A nonselective overall amino acid supplementation, however, has been reported to be beneficial in patients with alcoholic hepatitis.²⁰

Selective Roles for Proline, Tryptophan and Methionine-Choline

In contrast to patients with severe liver injury and PSE who may have increased circulating levels of aromatic amino acids, including tryptophan (see above), alcoholics with lesser liver involvement were found to have

decreased plasma levels of tryptophan, the serotonin precursor, and a decreased ratio of tryptophan over amino acids competing for transport into the brain.

In the rat, concomitant decreases in brain tryptophan and serotonin were noted.²¹ Central serotonin deficiency may contribute to the depressive status frequently seen in alcoholics. Changes that may contribute this decrease in tryptophan possibly include tryptophan pyrrolase, which is considered to be rate limiting for tryptophan catabolism. Rats fed alcohol chronically showed an increased activity of the enzyme in the liver and an increased formation of kynurenine after administration of a tryptophan load.²²

Proline has been implicated in the development of liver fibrosis because the hepatic-free proline pool size, which is involved in the regulation of collagen synthesis, may be increased by ethanol and is expanded in human cirrhosis. Indeed, in patients with alcoholic cirrhosis, increased serum-free proline and hydroxyproline have been reported.²³ In another study, plasma proline was found to be normal or even decreased and lactate elevations were less common.²⁴ When present under these conditions, hyperprolinemia may indicate degree of liver injury rather than fibrogenesis.

Methionine deficiency has been incriminated in the pathogenesis of liver injury for several decades. Its role as a lipotrope (together with choline) was first considered because in growing rats, deficiencies in dietary protein and lipotropic factors (choline and methionine) can produce a fatty liver. However, primates are far less susceptible to protein and lipotropic deficiency than rodents and clinically, choline treatment of patients suffering from alcoholic liver injury has been found to be ineffective in the face of continued alcohol abuse. Furthermore, massive supplementation with choline failed to prevent the fatty liver produced by alcohol in volunteer subjects.²⁵ Moreover, fatty liver, as well as fibrosis (including cirrhosis), developed in baboons despite liberal supplementation with methionine.²⁶

Methionine may also exert a more specific effect as a selective precursor of cysteine. Increased production of "free" radicals and acetaldehyde (from ethanol) by the "induced" microsomes can be expected to increase cysteine requirements, thereby acting as a drain on the methionine precursor. Furthermore, depletion of cysteine and the corresponding tripeptide glutathione may contribute to liver injury by promoting lipid peroxidation.²⁷

Precursor Lesions of Alcoholic Liver Cirrhosis

It is recognized that among alcohol users, there is a subpopulation which is particularly prone to develop alcoholism. Furthermore, not all heavy drinkers develop liver cirrhosis. There is at present a great need to find ways to recognize those predisposed individuals.

Genetic factors have been invoked as a basis for increased susceptibility. In the last several years, it has been proved that the predisposition for many different diseases is associated with specific histocompatibility antigens (HLA). There is, however, a conflict in the literature regarding their prevalence in alcoholic liver disease.

A less elegant but yet useful approach is the search for early precirrhotic lesions that could enable us to identify those individuals who have begun the fibrotic process and therefore stand the greatest chance of progressing towards cirrhosis. This search led to the realization that perivenular fibrosis represents an early sign of the fibrotic process. Individuals with perivenular and associated perisinusoidal and pericellular fibrosis in the liver were found to rapidly progress to full-blown cirrhosis if alcohol abuse was not brought under control.²⁸

With proper therapy, including support from community self-help groups such as Alcoholics Anonymous (AA), one can expect that the disease process can still be arrested at a relatively early stage. The form of nutritional therapy and to what extent it is beneficial at these early stages remains to be established.

Even when irreversible liver complications (such as cirrhosis) are already present and despite the severity of the condition, therapeutic intervention, primarily nutritional treatment, can alleviate major complications of cirrhosis, such as encephalopathy (which responds to protein restriction) and manifestations of portal hypertension, such as ascites (which respond favorably to salt restriction). At present, a major task is to avoid the development of these serious complications by diagnosing alcoholism and its complications at an early stage and arresting the disease process prior to the medical or social desintegration of the individual.

Summary

Alcohol remains a prevailing cause of malnutrition resulting in a variety of deficiency states secondary to decreased intake of nutrients. In addition to various well-described primary malnutrition syndromes, secondary malnutrition may result from the interference of ethanol with nutrient digestion, absorption or utilization.

Some of the latter alcohol-nutrient interactions have been recently defined and their pathogenesis is discussed here. Included are interactions with thiamin, folic acid, vitamin A and disorders secondary to amino acid imbalances. The rationale for various forms of therapy is reviewed, including the pitfalls of excess nutrient administration (particularly as it pertains to pyridoxine, vitamin A and amino acids). Desirability of recognizing early precirrhotic stages of alcoholic fibrosis is emphasized in order to start therapy prior to the medical and/or social disintegration of the alcoholic.

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The Role of Vitamin E in Clinical Medicine*

John G. Bieri, Ph.D.**

It has been more than fifty years since vitamin E was discovered, yet considerable mystique still exists as to its proper role in maintaining health and in treating various medical conditions. A large segment of the U.S. public is intrigued with the idea that supplementary vitamin E will have various benefits to health or fitness, and physicians often prescribe it for a variety of afflictions when no specific therapy is known. This review will attempt, in the light of current knowledge, to put into perspective the clinical effects of vitamin E deficiency and associated therapeutic treatments. This review does not attempt to address current research regarding the effects of vitamin E for normal individuals in counteracting cellular oxidation, mutagenic changes or immune responses. For more detailed information on the material discussed here, the reader is referred to several recent symposia and reviews.^{1, 2, 3}

Distribution and Dietary Intake

Vitamin E is one of the most widely distributed vitamins in foods. It is synthesized by plants, where it is found associated either with the lipid in cell membranes or concentrated in the more lipid-rich germ of seeds or in nuts.

The richest sources in our diet are the vegetable oils and the margarines and shortenings made from these oils, primarily soybean and corn oils. Refining of these oils results in variable losses of alpha-tocopherol (the most common form of vitamin E), but significant amounts still remain in the processed oils, margarines and shortenings. Whole grains, although not widely consumed in the U.S., can be a major source of total vitamin E intake. From plant sources, the vitamin finds its way into animal tissues and dairy products. Meat, eggs and dairy products have small amounts of vitamin E. Fruits and vegetables generally are low in vitamin E.

Studies in the U.S. have shown intakes for adults ranging from 5 to 15 mg of alpha-tocopherol equivalents (7.5-22 IU). Various international nutrition organizations have recommended that the vitamin E value in foods be expressed as milligrams of d-alpha-tocopherol equivalents rather than as international units.⁴ Generally, high fat diets will have more vitamin E than low fat diets. The Food and Nutrition Board of the National Academy of Sciences has recommended a daily allowance of 8 mg of alpha-tocopherol equivalents (12 IU) for women and 10 mg (15 IU) for men, but the allowance can vary according to the amount and type of dietary fat (discussed below) consumed.

Experiments in animals have shown that the requirement for vitamin E is increased with an increased dietary intake of polyunsaturated fatty acids (PUFA), primarily linoleic acid. It appears, however, that a significant interaction between vitamin E and PUFA occurs only at relatively high intakes of polyunsaturated fat. Sometimes

nutritionists express an unfounded fear that increased consumption of unsaturated fat (at the expense of saturated or animal fat) may jeopardize the vitamin E status of our population. This view overlooks the fact that sources of polyunsaturated fat in our diet are also the richest sources of vitamin E, as mentioned above. There is no evidence that any significant change in vitamin E status, as determined by plasma levels, has occurred over the past thirty years despite the trend toward a diet containing more unsaturated fat.

Absorption, Transport and Storage

Absorption of vitamin E is dependent on the person's ability to absorb fat. Studies in animals and human beings have shown that bile is essential for absorption.⁵ Esterified tocopherol (the form in most vitamin supplements but not found naturally) is readily hydrolyzed in the intestine, and only free tocopherol appears in lymph.

For maximum absorption, incorporation into mixed micelles in the lumen of the intestine is necessary. But at best, absorption is inefficient. Human studies yield 25% to 85% efficiency.⁶

When taken up from the intestine in lymph, tocopherol is transported to the circulation in chylomicrons and eventually is distributed to all lipoproteins, but primarily in low density lipoprotein or alpha-lipoprotein.⁷ It has been shown that the level of plasma vitamin E is highly correlated with total plasma lipids, total plasma cholesterol and low density lipoprotein.⁶

Circulating vitamin E is accumulated slowly by all tissues. In terms of absolute amounts, adipose tissue, liver and muscle account for most of the body's tocopherol. At any given daily dose, after a few weeks there is a constant concentration or a very slow rate of increase of tocopherol in most tissues, except adipose tissue in which the concentration continues to increase linearly.

In therapeutic terms, approximately a tenfold intake is required to double the plasma concentration. The content of tocopherol in human tissues varies widely with as much as a sixfold variation in adipose tissue.

Mechanism of Action

Vitamin E has long been known to be an effective antioxidant for stabilizing unsaturated fat against auto-oxidation, i.e., it protects them from oxidative breakdown and rancidity. There is wide agreement that tocopherol has a similar, although more complex, role in tissues. It is believed that the vitamin reacts with one or more damaging species of radicals—free radicals, active oxygen—thus protecting the vulnerable polyunsaturated fatty acids in cellular or subcellular membranes from destruction and ultimate tissue damage.

The effectiveness of vitamin E in protecting experimental animals against a variety of toxicants that are known to produce free radicals is one line of evidence for this theory. Clarification of the metabolic role of vitamin E, however, remains to be made.²

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Vitamin E Deficiency and Therapy

One of the enigmas in understanding the role of vitamin E in both health and disease has been the failure of the medical community to agree on the efficacy of vitamin E in treating any specific disease or abnormality. Although the vitamin has been prescribed sporadically over the years for a variety of human afflictions, the weight of medical evidence did not support these uses.

Among the conditions for which vitamin E has been prescribed are angina, muscular dystrophy, infertility, purpura, scleroderma and diabetes. Conditions still being investigated include cystic mastitis, certain types of ulcers and wounds, intermittent claudication and habitual abortion.

It should be noted that in all these studies, no patient was ever shown to be vitamin E deficient, and treatment was based on a postulated pharmacokinetic mechanism from mega-therapy.⁶ Many of these conditions have a variable history in any given patient and do not lend themselves to well-controlled studies. However, as long as a large number of patients claim an association between vitamin E therapy and improvement of these conditions, many physicians will continue to rely on this medications in lieu of a more rational treatment.

In contrast to the lack of agreement on the efficacy of vitamin E in the above conditions, there have been a significant number of reports in recent years in which treatment of patients shown to be deficient in vitamin E has produced improvement in certain aspects of their disease. These are patients who developed vitamin E deficiency because of an impaired ability to absorb fat. Included in this group are children with cystic fibrosis, biliary atresia and other disorders of the liver-bile system. Also included are older patients who have the genetic disease alpha-betalipoproteinemia (an inability to secrete beta-lipoprotein, the primary transport protein for tocopherol). After several years, a common feature of all these malabsorption diseases is impaired neuromuscular function, manifested by poor reflexes, impaired locomotion and changes in the retina of the eye.^{3, 8} Vitamin E replacement in these deficient patients has stabilized the existing condition which, untreated, often leads to death. Implementation of therapy when such diseases are first diagnosed should lead to marked improvement in life expectancy and quality of life for these patients.

Use of vitamin E in premature infants exposed to high oxygen atmospheres, continues to be explored as a means of preventing the blindness (retrolental fibroplasia) that often occurs. Unfortunately, vitamin E therapy does not entirely prevent this condition but will reduce its severity.⁹

It has been known for many years that premature infants are born in a relative state of vitamin E deficiency. Therapeutic trials have been made in an attempt to ameliorate some of their problems, such as intraventricular hemorrhage and hyperbilirubinemia.³ Results to date have been equivocal and further study seems warranted.

Recently, some patients with several genetic diseases that result in anemia (beta-thalassemia, glucose-6-

phosphate dehydrogenase deficiency, sickle cell anemia) have been found to have lower than normal plasma vitamin E concentrations.³ These are thought to be due to iron overload from repeated transfusions (iron is an effective destroyer of tocopherol). Supplementation of these patients with vitamin E has not shown any consistent effect on their clinical condition.

Normally, as mentioned earlier, the U.S. diet provides ample vitamin E. Numerous surveys over the past forty years have rarely documented apparently normal individuals who appear to be inadequate in this vitamin. Nevertheless, sizeable numbers of our population currently take large doses of alpha-tocopherol in the belief that some benefit will be obtained. Imagined benefits cover a wide range and are based mainly on a misinterpretation of animal experimentation. Included in perceived benefits are improved physical performance, stimulation of libido, improved complexion and prevention of aging. Although it is true that vitamin E-deficient animals may show some of these problems, there is no evidence that extra vitamin E in normal human beings will have any of these postulated effects.

Fortunately, vitamin E is a relatively nontoxic substance in contrast, for example, to vitamin A. A number of clinical reports, however, have documented problems in patients treated with anticoagulants when they self-dosed with large supplements of vitamin E.¹⁰ There appears to be an antagonism between vitamin E (or its oxidation products) and vitamin K, the latter being a critical component of the clotting mechanism. For most people, doses of 200 to 600 mg alpha-tocopherol daily appear to be innocuous, but we do not have sufficient information over a lifetime to say that such supplements are totally safe.

Summary: After fifty years of research on the role of vitamin E in health and disease, we know that patients with genetic diseases or congenital defects which cause malabsorption can develop vitamin E deficiency with associated symptoms. These are the only medical conditions where there is a consensus that vitamin E has a proven therapeutic role.

Many other clinical problems for which the vitamin is sometimes prescribed need further study to provide more convincing evidence of efficacy. Healthy persons receive an adequate intake of vitamin E in a balanced diet that meets other nutritional needs. Use of supplementary vitamin E by such individuals has not been shown to confer any additional health or fitness benefits.

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**As Soma relieves muscle spasm,
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patients are often able to resume
more normal activities.**

References: 1. Boyles WF, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions: thoracolumbar strain or sprain. *Today's Therapeutic Trends*, vol. 1(1), 1983. A controlled double-blind study of 71 patients. 2. Rollings HE, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions—thoracolumbar strain or sprain: A double-blind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. *Curr Ther Res*, vol. 34, Dec. 1983. A controlled double-blind study of 58 patients.

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For prescribing information, please see next page.

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INDICATIONS: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS: Porphyrin; allergy or idiosyncrasy to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

WARNINGS: *Idiosyncratic Reactions:* have appeared very rarely within minutes or hours after the first dose of carisoprodol. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation. Symptoms usually subside in several hours, but supportive and symptomatic therapy, including hospitalization, may be necessary.

Pregnancy and Lactation: Safe use has not been established; weigh potential benefits against potential hazards during pregnancy and lactation or in women of childbearing potential.

Usage in Children: 'Soma' — Not recommended under age 12.

Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g., driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive.

Drug Dependence: Use caution in addiction-prone patients.

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of carisoprodol.

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances.

Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock.

DOSAGE AND ADMINISTRATION: *Adults* — One 350 mg tablet 3 times daily and at bedtime.

OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used successfully with related drug, meprobamate.

HOW SUPPLIED: White, 350 mg tablets in bottles of 100 (NDC 0037-2001-01) and 500 (NDC 0037-2001-03).



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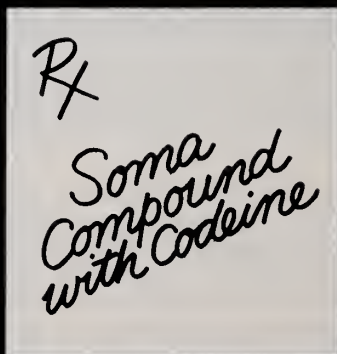
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ARTICULOS ESPECIALES

Worldwide Data Base: A Practitioner's Dream*

Ken Winikoff

It's a practitioner's dream: a medical data base, accessible throughout the world, using a uniform system that can be used for treatment by an internist in New York City or a physician in Nairobi.

The dream moved closer to reality this year through the ongoing work of a United Nations commission whose purpose it is to develop a system that will revolutionize healthcare and, more important, bring underdeveloped nations into the world of modern medical treatment.

The United Nations Committee on Emerging Nations Technology (UNACENT) was commissioned by the UN's World Health Organization in June, 1983, with a mission of researching evaluating, testing — and seeking financing — for a portable, computer-based medical information system.

The proposed data base, HELIX II, will be a multilingual index, composed of many specialized data bases, citation index, diagnostic research data, compiled lists, and a Product Information Exchange (PIE).

Initially, HELIX II will be available in English and French and soon thereafter in German, Spanish, African and Asian dialects.

Dr. Daniel Moody and Dr. Peter C. Tolos co-chair UNACENT. They were appointed because of their extensive backgrounds in telecommunications and information systems.

Moody has traveled throughout the world developing communications systems for the Agency for International Development and the Eminate of Djibouti, in eastern Africa, as well as city, state and federal systems in the United States. Tolos is executive director of TEC-HELIX, a respected independent consulting organization specializing in integrating information management systems with health services. He is also director of new products for the American Computer Association and has served as consultant for NASA, Lockheed and healthcare organizations.

The two have been traveling, testing equipment and conferring with professionals in line with a ten-phase program that will present a concrete proposal to a world conference to be held in San Francisco in four years. The amount of material to be evaluated is overwhelming and according to Tolos, has presented problems in meeting the commission's own deadlines.

Aided by Private Funds

"We're somewhat behind because we are looking for funding from primary sources — private institutions, foundations, grants," implying the problems involved with seeking public financing. "However, the hardware companies have been very helpful." Equipment evaluation has been aided by donations by manufacturers. "But even this phase is taking longer than anticipated because of the different configurations of systems," he said.

Although directly commissioned by the UN, UNACENT receives every little in the way of financial assistance from it. Most of the aid comes from the private, sector: hardware companies and medical services.

The Project Information Exchange, a data center providing information on medical products, has been a major contributor to UNACENT's work. Using PIE, a user can call up information about any medical product available and, if he wishes, can have additional information sent to him the push of a button.

Another problem Tolos cited was that of overcoming language barriers. "Our project involves the construction of a medical data base, which has a multiple language capability." UNACENT is looking into automatic translation (ALTS) and graphics, which are very important in overcoming the language barrier. The committee is also reviewing the Agnew Techtran, an automatic translation program. The system must be able to accommodate Roman, Hebraic, and Arabic alphabets. The problem is it just doesn't stop there.

"There's the old saying that if the flesh is weak, the spirit is strong. Well, translated literally into Russian, the phrase sounds more like: If the meat is bad, the vodka is good," Tolos said.

Although UNACENT is still in the initial stages of

*Reprinted from *Software in Health Care*, Feb/Mar 1984.

project implementation, including site identification, analysis and a tentative evaluated several hardware systems. Six configurations have been reviewed, and a total of 30 are expected to be examined.

The difficulties encountered in such a long-range plan are further heightened by a rapidly advancing technology that may leave some systems currently being evaluated obsolete by the final implementation stage. The commission is looking primarily at small, battery-powered units, including Kaypro and Otrona. The importance of a system lies in its ability to be learned thoroughly and rapidly, along with its ability to be operated away from existing power sources.

The committee realizes that most users will be relatively unfamiliar with computers and, therefore, it is paying close attention to those systems that require very little instruction for users.

"We're not bringing totally unfamiliar equipment and technology into remote areas," Moody said. "Most of the emerging nations have television, and we've just explained the system as a TV you can talk to. In some areas, where language produces an extreme problem, a joystick will most likely replace the keyboard," he added, noting that graphics are an integral part of any system facing a language problem.

Information Hard to Get

Although private enterprise has been most generous to UNACENT, Moody said, many developing nations have withheld vital statistics from the committee, perhaps due to embarrassment about conditions in that nation.

"The problems we're encountering are those I hadn't anticipated," he said. "Many emerging nations do not want to admit they've got (health) problems. Even if we promise to keep the information proprietary, they're hesitant — or misleading us. Some nations, particularly African nations, which have undergone a change of governments are willing to blame their deficiencies on previous administrations, but we'd like to have access to more information on a community level, not a bureaucratic level."

Moody cited China as a country which has no organized, national medical community. Although he has not met resistance from the Chinese government, he cited a lack of information available on a national level. Moody said the Chinese phase is perhaps the most exciting part of the project, given the lack of general information available.

Moody also hesitated to use individual-nation technology in transmitting medical information to users. He said he would like to use a UN satellite, should one ever be launched, to prevent the blocking of access by feuding nations. Citing the Iranian hostage crisis in 1980, he noted that if the data base was available at that time, there would have surely been a movement in this country to prevent access by the Iranian medical establishment until the hostages were released.

Food and medicine are two of the most politicized entities in the world. We're trying to avoid that in this project," he said.

UNACENT is adamant, however, about including all forms of medical practice in the global data base. Such

practices as shamanism, acupuncture and other treatments frowned upon by western medicine, will be included for evaluation by users.

"It's not our concern to evaluate medicine," Moody said. "DMSO and its uses will be included — with reported results, of course — as well as the use of marijuana for treatments such as glaucoma." Also, many drugs not approved in the United States, but available in foreign countries, will be indexed in the system. Moody admitted this rule has met with a some what cold response from the medical establishment in the United States, but underlined his determination to keep the HELIX II data base completely free of political influence.

HELIX II will not provide diagnoses for medical users. It will, however, make available any paper or study once it has been published and entered into the public domain.

The two co-chairmen, who oversee the activities of some 13 different subcommittees in UNACENT, have a concrete idea of the type of data base they would eventually like to see available for a pilot test scheduled for 1987. Although the test site has yet to be determined, it will most likely be in the most testing of environments, one chosen for its remoteness and one which will most tax the hardware and the visions of the commission's leaders.

In the meantime, Moody and Tolos continue their travels, seeking further support, surveying potential test sites, and addressing the medical communities around the world in hopes of obtaining more vital information needed to design and implement the system.

Checking his calendar, Moody noted that in addition to his visits to South America and Africa, he will be visiting China in November and Southeast Asia shortly thereafter, and added that his domestic schedule includes addressing the National Conference on Computers and Medical Practices in San Francisco later this year.

Although he admits to being set back a bit by a number of factors, some of which are political in nature, he seemed unfazed and remained certain that the commission would meet its 1987 test deadline.

"It may sound funny but I actually planned on these delays," he said. "When I'm asked how we're progressing. I say, We're behind schedule as planned."

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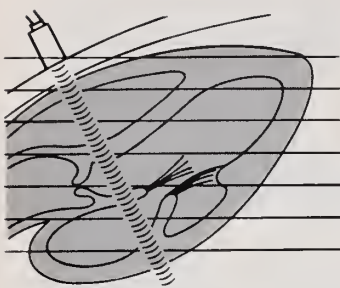


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ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., FACC
Hugh D. Allen, MD, FACC
Celia J. Flinn, MD

This 8-year-old boy was asymptomatic and active. He was studied utilizing a Honeywell echocardiograph (Biosound Corp. Indianapolis, Ind.) and pulsed (ranged-gated) Doppler, with 2.25 MHz and 3.5 MHz off-axis suprasternal transducers, and a continuous wave (CW), angled M-mode suprasternal transducer (Irex echograph- Ramsay, NJ). Traces were digitized and blood flows calculated on an Apple II Plus computer (Apple Computer Inc. Cupertino, CA) and a disk from a prepared program (Biodata. Davis, CA).

See Figures 1-4.

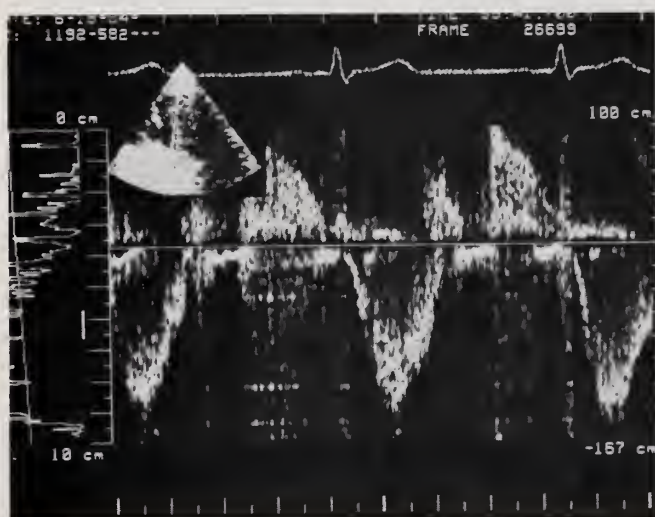


Figure 1

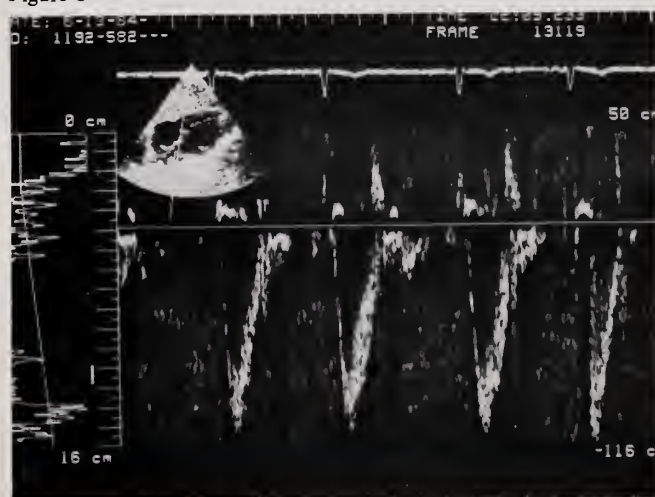


Figure 3

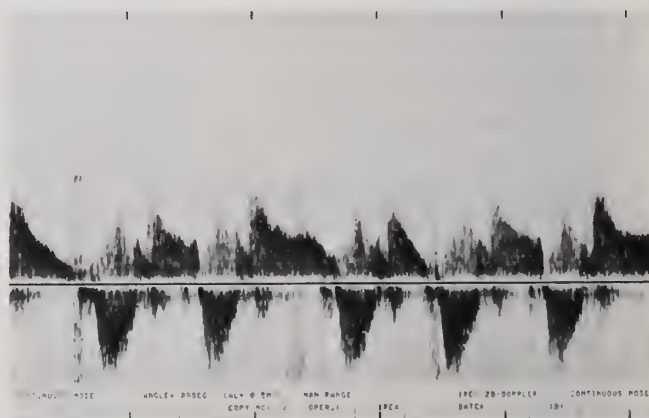


Figure 2

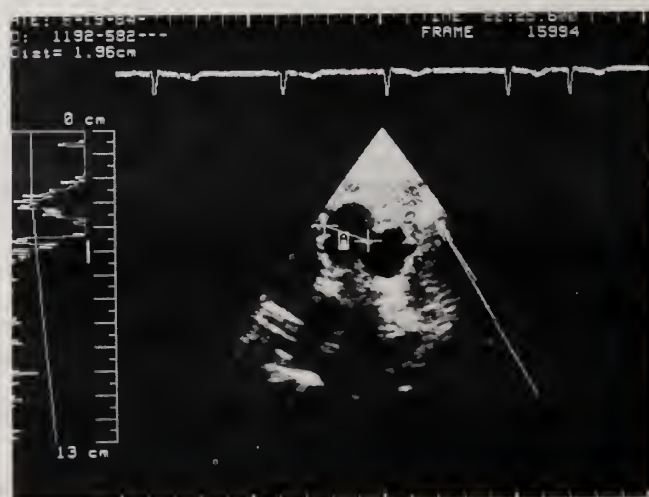


Figure 4

Questions

1. What are the diagnoses?
2. Calculate blood flow velocities, aortic and pulmonary blood flows (cardiac outputs), vessel areas and pulmonary artery pressure.
3. What is the severity of the lesion?

Answers

Pulmonary Regurgitation (PR). May conform to **Idiopathic Dilatation of the Pulmonary Artery (IDPA).**

Figure 1. Honeywell Doppler. Parasternal short axis view. 2-D echo to place sample volume (SV) in pulmonary artery (PA), as shown on upper left 2-D insert, with cursor course. Systolic negative PA flow (TFF); diastolic positive flow (RF) indicating PR.

PA flow velocity (V)- Peak = 160 cm/S (Normal 63-76 cm/S, range 50-105, in children).

Mean = 38 cm/S.

PA flow (TFF) = 8300 cc/min. PA diameter = 2.15 cm; vessel area 3.6 cm²

RF (PR = 5000 cc/min. Peak V = 100 cm/S and mean V = 23 cm/S.

NFF = 3300 cc/min.

Pulmonic valve RFr = $\frac{500}{8300} = 60\%$, or $\frac{8300-3347}{8300} = 60\%$.

Using tricuspid valve flow (3347 cc) as pulmonary forward flow or NFF.

Time-to-Peak Velocity (TPV) = 80, 100, 120 mS, indicating no or minimal pulmonary hypertension (PH).

Figure 2. Irex CW. Doppler transducer in suprasternal notch (blind).

Systolic negative PA flow (TFF) = 10,147 cc/min. Peak V = 1.9 M/S, mean 50 cm/S.

Diastolic positive flow (RF). Peak flow V = 1.9 M/S, mean 55 cm/S.

By CW, RFr = $\frac{10147-3347}{10147} = 67\%$.

By Irex CW Doppler, the TFF and the RF appear equal, which would be impractical.

Figure 3. Honeywell Doppler. Subcostal 4-chamber view. SV in left ventricular outflow tract.

Aortic flow (systolic negative) - Peak V = 113 cm/S, mean 29 cm/S.

Vessel area 3 cm². 5280 cc/min (cardiac output).

Figure 4. Honeywell. 2-D. Short axis.

Ascending aorta dimension 1.96 cm. PA is to left and inferior.

Discussion

Primary PR is due to a variety of lesions, and may be associated with IDPA.

Pulsed and CW doppler echocardiography applying fast Fourier transform (FFT) spectral analysis (which has replaced zero crossing method and time-interval histograms) offer a rapid, accurate means for measuring blood flow in the aorta, PA, cardiac chambers, septal defects and shunts, etc. 2-D echo provides guidance for placement of the pulse Doppler SV, and measurement of valve and vessel diameters for determination of areas. Once flow velocities are determined, total blood flow (cardiac output), valvular and aortic gradients and areas are calculable, all expeditiously. Valvular regurgitation, with quantification, can be evaluated.

Flow velocity (V), in cm/S =

$$\frac{fc}{2 f^0 \text{ Cosine } \theta}$$

Where f = Doppler frequency shift.

f^0 = frequency of emitted ultrasound in HZ.

C = velocity of sound in tissue (1540 M/S).

θ = angle between emitted ultrasound and axis of blood flow (beam-flow or intercept angle).

The transducer is oriented parallel to blood flow (<20°) so as to make θ as near 0° as possible (cosine of 0° = 1). Mean velocity is determinable by computer.

Flow = mean V/beat x beats/min x orifice area
Cosine θ

OR mean V in cm/S x flow area in cm² x 60 S/min
Cosine of the intercept angle θ

Area of a circle = πr^2 ; radius (r) =

$$\frac{\text{diameter}}{2}$$

PR typically manifests a characteristic audio signal and wide frequency spectral dispersion. The PA shows an increased velocity and systolic flow disturbance.

The degree of PR (or aortic regurgitation), i.e. the RFr with pulsed or CW Doppler (SV in right ventricular outflow or PA), may be quantitated as:

$$\frac{\text{regurgitant flow (RF x 100) or}}{\text{total forward flow (TFF)}}$$

$$\frac{\text{TFF - NFF (net forward flow)}}{\text{TFF}}$$

With the probe in the high parasternal short axis position, flow away from the probe during systole (negative on the time-velocity curve) reflects TFF which is the NFF plus the RF (diastolic positive flow toward the probe).

PA pressure- PH, may be determined from Doppler PA velocity traces (Honeywell echocardiograph) as:

- 1) an absence of the normal presystolic "a dip" (similar to absent "a wave" of M-mode echo).
- 2) Time-to-peak velocity TPV (time between onset and peak of PA velocity curve). Normal 106 mS; PH 106 mS.
- 3) PA pressure = $80 - \frac{\text{TVP}}{2}$

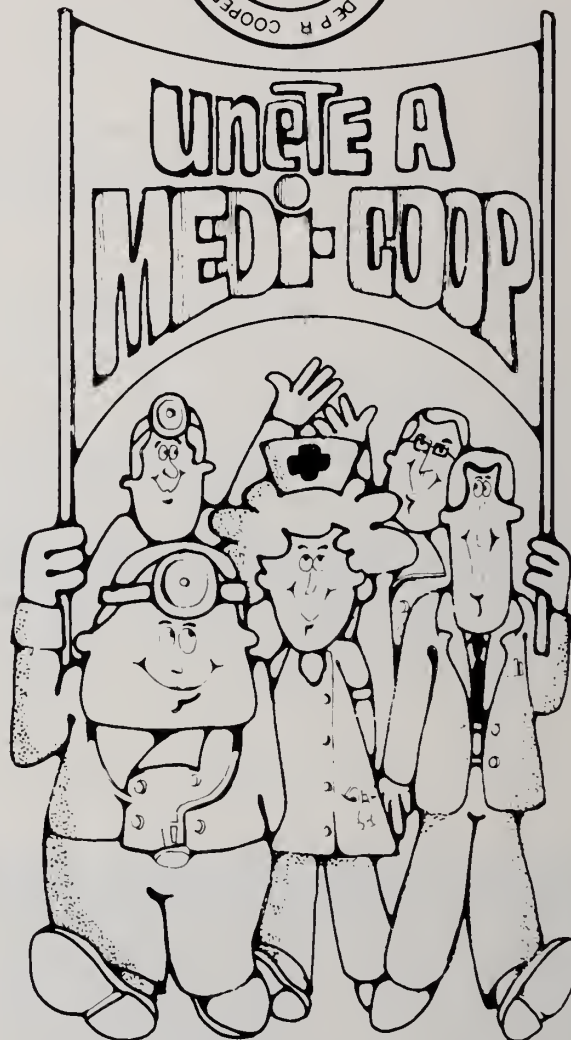
- 4) spectral broadening. Spike and dome contour, etc.

In PR due to an abnormality of the pulmonic valve itself and normal PA pressure, the velocity of the PR falls gradually during diastole; in secondary PR from PH the velocity remains constant throughout diastole. The magnitude of velocity depends upon severity of the PH.

Bidimensional and doppler echocardiography have proven to be extremely useful, reliable and essential for the rapid diagnosis, management and follow-up of patients of all ages and types of congenital heart disease. It is especially valuable in the differential diagnosis and acute management of the critically ill neonate and infant. It is invaluable in the postoperative patient. In PR, doppler is more sensitive and reliable than phonocardiography.

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Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak lolic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperurcemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

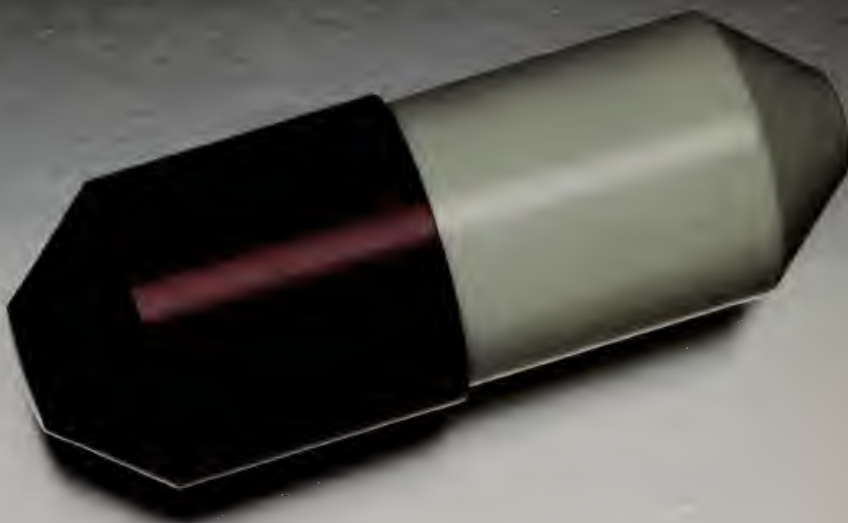
Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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American College of Cardiology

DIAGNOSTIC, THERAPEUTIC POTENTIAL OF ANTIBODIES IN CARDIOLOGY

Specificity and selectivity are the keys to optimal diagnosis and therapy. According to Edgar Haber, M.D., F.A.C.C., of Massachusetts General Hospital in Boston, antibodies have the potential to provide both specificity and selectivity as diagnostic and therapeutic agents.

"Of all classes of compounds," Dr. Haber says, "antibodies provide the greatest range of specificities and affinities. The number of interatomic interactions between an antibody combining site and a large ligand, such as a receptor, far exceeds those between the common small ligand or drug and its corresponding binding site. Increased selectivity and affinity result."

With all the potential antibody specificities that exist, finer selectivity can be created. As Dr. Haber says, "Modern studies in the molecular genetics of antibody synthesis indicate that, potentially, there are at least 10 billion different antibody specificities." Theoretically, this should permit the selective recognition of almost every structure in the human body.

Our ability to make and use antibodies is growing at an explosive rate. While in the past their only source was an immunized animal, now antibodies can be produced in vitro in mammalian cell culture by amplifying a single antibody producing clone. Clones of antibody producing cells secrete single antibodies that may be considered pure chemicals. With recent methods to produce antibodies in industrial fermenters on a large scale, Dr. Haber says, "It will not be too long before mammalian cells will be replaced by yeast or bacteria, through the application of recombinant DNA methods, so that antibodies will be produced as readily as penicillin."

Solutions to the problems in the use of antibodies as diagnostic and therapeutic agents are in sight, says Dr. Haber. Two clinical studies already have employed Fab, a smaller fragment of the immunoglobulin molecule, and smaller antibody fragments reduce the risk of immuno-

genecity. Human immunoglobins may now be produced by cell fusion techniques in vitro, and immunoglobulin genes are now routinely cloned for study.

"It is not at all far-fetched to envision their manipulation and expression as antibody fragments carrying the minimal structure necessary to effect antigen binding. Recombinant DNA methods permit the introduction of human immunoglobulin framework sequences so that tolerance to intrinsic proteins can prevent the mounting of an immune response," he says.

Some of the applications of antibodies in cardiology that Dr. Haber discussed included adrenergic-receptor blockade, renin-specific antibodies, treatment of digitalis intoxication, evaluation of myocardial infarct size and visualization of thrombi in vitro.

Dr. Haber described how the well-known immunologic principle of raising antibodies specific for another antibody's combining site (anti-idiotypic antibodies) can be used as the vehicle for molding a desired shape. In his experiments, Dr. Haber selected antibodies that recognized common structures on all betaadrenergic agonists and antagonists. These antibodies were "receptor mimics" in that they bound all compounds that would interact with the beta-adrenergic receptor but did not interact with similar compounds. "A second generation of antibodies (anti-idiotypic antibodies) was then raised using the first antibodies as immunogens," Dr. Haber explains. "The anti-idiotypic antibodies were selective beta-receptor blockers as shown by their ability to compete with beta-blocking drugs as well as by inhibition of the generation of adenylate cyclase in response to stimulation by isoproterenol.

These receptor-specific antibodies could potentially be used: (1) to recognize structural differences among subsets of beta-adrenergic receptors; (2) in the examination of their physiologic roles using reagents of greater resolution, (3) in the isolation of receptors with antibody affinity chromatography, and (4) as antibody fragments that are highly selective drugs.

In earlier studies, Dr. Haber and his colleagues showed purified polyclonal renin-specific antibodies and their Fabs were effective renin-blocking agents in experimental animals. "Monoclonal antibodies to human renin now are available," says Dr. Haber, and they "may provide the potential for using a highly selective renin blocker in examining the question of the role of renin in human essential hypertension, a question that is still largely unsettled."

Another application of antibodies in cardiology Dr. Haber discussed included the use of a digoxin-specific antibody in the clinical reversal of toxicity, an all too well-known adverse drug reaction. "We reasoned that if an antibody specific to the digitalis glycosides had a higher affinity for the drug than the physiologic receptor, it should be possible to transfer the ligand from the receptor to the antibody. If Fab rather than intact antibody were used, the antibody-drug complex would be rapidly excreted in the urine," Dr. Haber says. In a multicenter trial involving 26 patients with life-threatening digitalis intoxication, Fab dramatically reversed the signs and symptoms of intoxication, without hypersensitivity manifestations.

In another application of antibodies, Dr. Haber and his co-workers are studying ways to quantify infarct size. "Initial clinical studies have shown substantial promise that a highly selective method may be developed for imaging and eventually sizing myocardial infarcts," says Dr. Haber, "a method that may be valuable in assessing methods to evaluate reperfusion therapy following coronary thrombosis."

Recently, two researchers in Dr. Haber's laboratory created a specific monoclonal antibody that reacted exclusively with fibrin. Mice were immunized with a synthetic peptide, not with fibrinogen, that contained the amino acid sequence of the beta chain of fibrin at the point of thrombin cleavage. "Thrombin, which cleaves both the beta and alpha chains of fibrinogen, reveals two new amino terminal ends and, thus, two new antigenic sites. Because these sites represent such a small part of the total fibrin molecule, they do not seem to give rise to specific antibodies when immunization with the entire fibrin molecule is undertaken," Dr. Haber says. "However, by emphasizing a single antigenic site through peptide synthesis, the immune response can be directed at the difference between fibrin and fibrinogen."

In experimental animals, these monoclonal antibodies have been shown to localize in thrombi. "The exciting promise of this work is not only in the delineation of thrombi in both arteries and veins, but also the potential to detect ulcerated atherosclerotic plaques that characteristically have superficial fibrin deposits," Dr. Haber says.

"It may one day be possible to map potentially troublesome arterial lesions *before* thrombosis occurs. We are on the brink of developing a new pharmacology based on the unique resolution of the antibody combining site," he says.

FINDINGS ON CORONARY ANGIOSCOPY DURING CARDIAC CATHETERIZATION PRESENTED

Coronary angiography may be a novel way of viewing the coronary artery, but a longer and more flexible angioscope—and therapeutic application—must be designed before the procedure finds its clinical niche, according to J. Richard Spears, M.D., F.A.C.C.

Dr. Spears, Assistant Professor of Medicine and Radiology at the Harvard School of Medicine, Cambridge, MA, reported his findings in a paper titled "Coronary Angiography during Cardiac Catheterization."

Dr. Spears says he and his colleagues reasoned that coronary angiography should permit direct inspection of the lumen cross-section and identification of lesion pathology. The researchers decided to test the feasibility of introducing a #5F Olympus Ultrathin fiberscope into the obstructed right coronary artery in five patients following routine cardiac catheterization by the brachial approach.

An 8.3F USCI woven Dacron angioplasty guiding catheter was modified to enlarge its lumen.

In three patients the coronary lumen was viewed after displacing blood with approximately 5-10 cc of a

translucent crystalloid solution. White atheromatous plaque was seen at the site of obstruction. In 2 patients, lack of sufficient flexibility in the distal 2 cm of the angioscope prevented passage to the catheter tip, Dr. Spears says.

"We saw the stump of the right coronary artery in 3 patients out of 5," Dr. Spears says, "but the problem is lack of flexibility in the tip of the angioscope."

"The sharp right angle turn built into preformed catheters would make it impossible to enter by the femoral approach with this catheter," Dr. Spears adds.

"The research in itself is fascinating. It (the technique) could provide clues to pathophysiology, and has many potential research applications," Dr. Spears says. For example, Dr. Spears says, in the event of abrupt reclosure after balloon angioplasty, viewing the coronary lumen might be helpful. Or, the technique could be used to differentiate a residual thrombus from plaque.

However, Dr. Spears says, "for a clinical application, it would be useful only if we can couple it with a therapeutic modality." He adds, "And I'm not optimistic about its therapeutic potential."



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HEART DISEASE DRUG MAY BE USED FOR CANCER

A drug now used to treat heart disease also prevents cancer from spreading in laboratory animals, according to researchers at Wayne State University.

A two-year study has shown that the drug nifedipine inhibited formation of lung tumors by about 80 percent in mice injected with tumor cells. The drug represents a new approach for cancer therapy, according to Dr. John D. Taylor, chairman of the University's Department of Biological Sciences. Discussions now are underway about testing nifedipine on humans.

CANCER-CAUSING CHEMICAL MAY INHIBIT IMMUNITY

The ability of benzo (a) pyrene (BP), a known cancer-causing chemical, to induce lung tumors in laboratory mice is paralleled by its ability to inhibit the activity of the immune cells known as T lymphocytes, according to Lee M. Blum and Dr. Anthony J. Triolo of Thomas Jefferson University, who reported that mice which are resistant to BP-induced lung tumors are also resistant to immunosuppression. They added that further research is needed to find out if immunosuppression is a cause or an effect of BP-induced cancer.

The immune system protects the body from invasion

by foreign particles, such as viruses and bacteria, and rids the body of abnormal tissue, such as cancerous cells. Yet occasionally, some cancer cells successfully elude the immune system to gain a foothold in the body.

While scientists do not understand how cancers avoid immune rejection, they have speculated that a defect in the immune system may, in some cases, be responsible. Clinical observations have made it clear that people treated with immunosuppressive drugs and patients with immunodeficiency diseases have a predisposition for developing cancer.

BP is ubiquitous in our environment. It is created by the incomplete combustion of fossil fuels and as a by-product of coal conversion processes. Not surprisingly, BP is also found in cigarette smoke. Scientists have found that in addition to its carcinogenic effects, BP is capable of suppressing immune responses in laboratory animals.

Blum and Triolo administered single oral doses of the carcinogen to laboratory mice belonging to three different strains. These strains all have different susceptibilities for the development of lung tumors. Fourteen weeks after BP administration, the animals' lungs were examined for tumor development.

At the same time, the investigators analyzed the animals' immune competence, testing the humoral immune response and the cell-mediated response. The first response indicates the animal's ability to form antibodies against a foreign molecule. The cell-mediated response is determined by testing the activity of T lymphocytes.

The Philadelphia researchers found that the ability of BP to cause lung tumors paralleled its ability to suppress the cell-mediated immune response. Animals with the highest number of lung tumors after BP treatment also had the greatest amount of lymphocyte suppression. Animals resistant to BP-induced lung tumors showed to immunosuppression. BP treatment had no significant effect on the humoral immune response.

Blum and Triolo concluded that while their results are preliminary, they do suggest that cell-mediated immunity may play some role in the body's defense against carcinogenesis induced in the lung by chemicals such as benzo(a)pyrene. Of course immunosuppression could have been the result of tumor development. Additional research into that possibility will be needed.

DOG TESTS SHOW DAILY EXERCISE PROTECTS THE HEART

Daily exercise may improve heart function and protect heart attack patients from sudden cardiac death, the leading cause of death throughout the industrially developed world.

Physiologist Dr. George E. Billman of Oklahoma University Health Sciences Center based the suggestion on research with laboratory dogs susceptible to ventricular fibrillation, the "electrical accident" that leads to sudden cardiac death. After a six-week exercise training program, these animals were completely protected from ventricular fibrillation. Dr. Billman noted that

protective effect was lost in two dogs removed from the training protocol and given six weeks of cage rest.

In the United States, sudden cardiac death claims nearly 1200 victims daily—almost one person every minute. Sudden death in these people is almost always caused by a cardiac electrical derangement leading to ventricular fibrillation, referred to as VF for short. During VF each heart muscle cell contracts in an uncoordinated fashion, preventing the movement of blood from the heart.

In research supported by the National Institutes of Health, the Oklahoma scientist worked with two groups of laboratory dogs, one of which was particularly vulnerable to ventricular fibrillation. Experiments with the dogs suggested that a fundamental difference in the nervous regulation of the cardiovascular system existed between the two groups. Vulnerable dogs, which could always be thrown into ventricular fibrillation with a blood flow occlusion procedure, showed only a small heart rate change—a 16 beat-per-minute decrease—in response to an increase in arterial blood pressure. But the other dogs, which rarely exhibited sudden death, showed a 58-beat-per-minute decrease in heart rate in response to an arterial blood pressure increase.

The difference between the two groups of dogs provided the Oklahoma investigators with a model for studying ways to prevent ventricular fibrillation. And it suggested that a treatment which compensates for this difference may protect against fibrillation.

The treatment chosen was exercise training which has been shown to alter the nervous control of heart function. Exercise training will reduce resting and working heart rate. Aerobic exercises, such as running, have recently been used quite successfully to rehabilitate patients recovering from heart attack.



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U.S. UNIVERSITY HOSPITALS TECHNICALLY INTENSIVE, COSTLY

University hospitals in the United States have reached a level of technology and specialized care that may not be sustainable, suggests a study by a University of California, San Francisco researcher.

Writing in the July 13 issue of JAMA, Steven A. Schroeder, MD, says there is concern that U.S. university hospitals may be achieving results that are technically excellent but financially unrealistic. Schroeder compared four major European University Hospitals: Leuven, Belgium; Klinikum Steglitz, West Berlin; Leiden, the Netherlands; and St. Thomas', London; with the University of California in San Francisco (UCSF).

The study showed that UCSF's costs per bed were 2.2 to 3.5 times higher, its inclusive per diem charges at least four times higher, and its malpractice premium at least 50 times greater. "Overall, European hospitals are larger, less expensive, less technology intensive, staffed by fewer employees and physicians, occupied by less severely ill patients, and more apt to serve as regional referral centers," Schroeder concludes. The European hospitals also had more explicit rationing of care according to age and severity of illness, he says. The study also revealed that Steglitz and UCSF had the largest number of severely ill patients of the five hospitals. Schroeder reports, "In the other three hospitals, several [resident physicians] volunteered that their approach to serve illness was much less aggressive than they had observed in the United States or West Germany and that their hospitals placed greater stress on 'quality of life' issues." As examples, Schroeder says patients with cancer in whom end-stage renal disease developed would probably not undergo dialysis, and patients with metastatic cancer probably would not receive chemotherapy.

Of the five hospitals, UCSF had the highest proportion of intensive care beds (8.2 percent), but Schroeder notes this was still below the 1981 median for U.S. university owned teaching hospitals (11.4 percent). "This investment in intensive care, which may be the most sensitive marker of a hospital's technology intensiveness, seems to be a characteristic of U.S. medicine as a whole...levels of CT scanner provision, coronary artery bypass surgery, and therapy for end-stage renal disease far exceed those of all other Western countries," he adds.

Schroeder suggests two strategies for American University Hospitals: decreasing costs through (1) greater rationing of equipment and services and (2) regionalization of highly technical care.

OVERALL INFANT MORTALITY DROPS BUT SUDDEN INFANT DEATH RISES

Overall postneonatal mortality (PNM) rates in the United States have declined dramatically in recent years, by almost half among black infants. But reported rates of sudden infant death (SID) have increased drastically during the same period, making it the leading reported cause of death in infants aged four weeks to 12 months. These statistics from the Centers for Disease Control are reported in the July 20 issue of JAMA.

Muin J. Khoury, MD, and colleagues studied National Center for Health Statistics birth and death certificate data for 1962 through 1978. They found that most of the decline of PNM can be accounted for by reduced mortality from infectious diseases, especially respiratory illnesses. Infant deaths attributed to birth defects and to injuries, except homicides, also decreased. Many deaths are related to socioeconomic conditions and access to medical care, underscoring the importance of ready access to care, the researchers say.

The overall rate of PNM in the United States, although declining, is higher than levels reported in Scandinavian countries, the researchers note, and it appears related to the high reported incidence of SID. "Although in the 1960s SID accounted for a negligible proportion of postneonatal deaths, it emerged in the 1970s as the leading reported cause of PNM, accounting for about one third of all deaths in 1978," they say.

"On death certificates, however, SID may represent a diverse group of conditions, and its reporting has been subject to criticism in case definitions and ascertainment," the researchers note. There is some question whether earlier reports of infectious respiratory disease death may have actually been SID. "It may well be that SID has always been an important, although unrecognized, cause of PNM."

With recent improvements in the reporting methods, the researchers suggest, better estimates of the true incidence of SID will be obtained. They conclude, "The massive increase in the rates of SID, although partially explained by coding or reporting phenomena, warrants active pursuit for a better pathophysiologic and etiologic delineation of the entity."

CHICKENPOX VACCINE SAFE FOR LEUKEMIA PATIENTS

Children with leukemia in remission may be safely and successfully immunized against varicella, commonly called chickenpox, even if they are receiving chemotherapy, suggests a study reported in the July 20 issue of JAMA.

Anne A. Gershon, MD, of New York University Medical Center, and colleagues immunized 191 children susceptible to chickenpox who had leukemia in remission. The researchers report serological evidence of an immune response in approximately 80 percent of the children after one dose and in more than 90 percent after two doses. Forty-two of them had completed chemotherapy treatment one to 12 months before vaccination; 149 had maintenance chemotherapy suspended one week before and after vaccination. The researchers say the major side effect was a mild to moderate rash, especially among the chemotherapy patients.

Twenty-one of the vaccinated children later and household exposures to varicella or zoster. The attack rate among these children was 18 percent, which is significantly lower than the usual 90 percent rate, the researchers note. "All cases of clinical illness were extremely mild," they say, which was clearly different from cases of varicella among normal children or among unimmunized children receiving chemotherapy for leukemia.

"The severity of varicella in children with an underlying malignant condition receiving chemotherapy is well recognized," the researchers say. Earlier reports suggested that without immunization or antiviral chemotherapy, about 30 percent of children with an underlying malignant condition who contract varicella experience severe symptoms, and at least seven percent die.

The researchers point out that no cases of even moderately severe varicella occurred after immunization in this group of leukemia patients. They add, "Our studies of almost 200 children, most of whom were receiving chemotherapy, strongly suggest that varicella vaccine is safe as well as effective to administer to these immunocompromised persons."

EXERCISE LOWERS CHOLESTEROL LEVELS

Weight-training exercise results in favorable changes in lipid and lipoprotein levels in previously sedentary men and women, according to a study from the Oregon Health Sciences University in Portland. Linn Goldberg, MD, and colleagues writing in the July 27 issue of JAMA report on a prospective study involving eight women with an average age of 27, and six men, average age 33, who underwent 16 weeks of weight-training exercise. Women demonstrated a 17.9 percent decrease in low-density lipoprotein cholesterol; men showed a 16.2 percent decrease.

COOL DOWN AFTER EXERCISE

An Atlanta Braves team physician, John D. Cantwell, advises athletes to "cool down" after exercise. Writing in the Questions and Answers section of the July 20 JAMA, he says cold showers should be avoided after vigorous exercise, and adds that the Braves typically spend up to 15 minutes unwinding after a game, having "light refreshments," before heading for the showers.

TREATMENT SUCCESS WITH INTERFERON

A patient with acute myeloblastic leukemia and extensive herpes simplex virus infection was treated successfully with human leukocyte interferon and minimal doses of cytarabine hydrochloride. "Complete and rapid healing of skin lesions with remission of the leukemia occurred during 15 days of therapy," say Yoseph Shalev, MD, and colleagues of Israel's Kaplan Hospital, writing in the July *Archives of Dermatology*.

STUDIES CONFIRM EXERCISE REDUCES RISK OF HYPERTENSION

Two articles in the July 27 JAMA provide clear evidence that regular physical exercise can reduce the risk of high blood pressure.

Steven N. Blair, PED, of the University of South Carolina, Columbia, and colleagues measured physical fitness by treadmill testing of 4,820 men and 1,219 women aged 20 to 65 years. All were free of cardiovascular disease and had normal baseline blood pressure levels; follow-up was done between one and 12 years (median, four years). The researchers found that, "After adjustment for sex, age, follow-up interval, baseline blood pressure and baseline body mass index, persons with low levels of physical fitness (72 percent of the group) had a relative risk of 1.52 for the development of hypertension when compared with highly fit persons."

The researchers found that baseline blood pressures were also highly predictive of hypertension risk. "Even patients in the normal range (120 to 129 mm Hg systolic and 81 to 84 mm Hg diastolic) had almost a threefold increase in risk over subjects with lower baseline levels," they report. When these normal levels were found in physically unfit persons, they add, the risk increased to four times the risk for highly fit subjects in the lowest blood pressure category.

The researchers note that their findings of an overall excess risk of 52 percent for persons with low levels of fitness is somewhat higher than the 35 percent excess risk reported by Paffenbarger and colleagues in 1983. That study compared Harvard alumni who did and did not participate in vigorous sports play in middle age.

Also in the July 27 JAMA is an extended report on the Harvard study. Ralph S. Paffenbarger, Jr., MD, DPH, of Harvard University School of Public Health, and colleagues examined personal athletic activity as it related to coronary heart disease among 16,936 Harvard alumni. The current study showed a 49 percent excess risk of coronary heart disease among those who were less active. The alumni reported stairs climbed, city blocks walked, and time and type of sports actively played each week.

"Habitual postcollege exercise, not student sports play, predicts low risk," the researchers say. "Sedentary alumni, even ex-varsity athletes, have high risk. Sedentary students becoming physically active alumni acquire low risk." The researchers add that exercise benefit is independent of contrary life-style elements such

as smoking, obesity, weight gain, hypertension, and adverse parental disease history. "Hypertension is clinically the strongest predictor of coronary attack, but inadequate exercise is strongest on a community basis," the researchers conclude.

The findings are based on 572 first heart attacks among 16,936 Harvard alumni, from 1962 to 1972, and 1,413 total deaths, from 1962 to 1978.

REDUCED SEX HORMONES FOUND IN MALE ENDURANCE RUNNERS

Men who regularly run more than 40 miles each week experience reduced levels of testosterone and prolactin when compared to nonrunners, according to a report in the July 27 issue of JAMA.

Observations of altered endocrine function in women runners have previously been reported in the medical literature, but information about chronic effects of endurance training on pituitary-gonadal function in men has been scant.

Now, Canadian researchers Garry D. Wheeler and colleagues from the University of Alberta, Edmonton, have tested 31 men who regularly run 40 or more miles each week and 18 sedentary men for sex-related hormones. Total testosterone and free testosterone levels were significantly lower in runners than in nonrunners. Only four of 31 runners had total testosterone levels above the mean for sedentary men. Prolactin, a hormone necessary for normal manufacture of sex steroids within the testis, was also significantly lower in runners, according to the researchers.

They note that men, unlike women, do not possess a critical dependence upon a daily, cyclic pattern of endocrine regulation of the reproductive system. Consequently, they suggest that the reproductive capacity of men would be less likely to be influenced by minor alterations in reproductive hormone levels. However, the researchers note that they "are unaware of any definitive study of the effect of endurance training on sperm production."

Reduced testosterone levels have been observed with physical and psychological stress, the researchers note. They suggest that lower testosterone levels may be part of a decreased libido some runners report during intense training, but they add that chronic fatigue may also be a factor in endocrine changes. They cite a study of soldiers in a five-day combat-training course who had temporarily lowered testosterone and prolactin levels but who had normal levels after brief periods of sleep. The researchers note, however, that the runners in their own study had slept normally and had not trained in the 24 hours before testing.

The researchers conclude that "if the observed differences are not solely population specific, both the mechanism(s) by which endurance training may induce lower sex steroid and prolactin levels, and the implications, physiological and perhaps pathophysiological, remain to be explored."

In another current JAMA article discussing runners,

James A. Blumenthal, PhD, and colleagues from the Duke University Medical Center report on a study comparing personality traits and behavioral dispositions of compulsive runners and patients with anorexia nervosa. Anorexia nervosa is a behavioral syndrome of self-starvation most often affecting young women.

The hypothesis that anorectic persons and compulsive men and women runners share a common set of personality traits was tested by the Durham, NC, researchers. They analyzed results from Minnesota Multiphasic Personality Inventory tests completed by 43 runners and 24 anorectic patients. Their findings: compulsory runners do not suffer from the same degree of psychopathology as anorectic patients. Their data are, in fact, "consistent with other reports that suggest that people who engage in regular exercise are essentially well adjusted and cope with stress effectively," they conclude.

ANEURYSM MAY PRESAGE GREATER CANCER RISK

Patients with aneurysms of the abdominal aorta appear to be at greater risk of developing cancer, according to a new study from Yale University School of Medicine.

Writing in the July *Archives of Surgery*, M. David Tilson, MD, and colleagues report that 38 patients with aortic aneurysms were found to have cancer five to ten years after surgical repair.

By contrast, only 13 percent of a control group of 61 patients who experienced surgery for atherosclerotic occlusive disease had cancer five to ten years after surgery.

"The crude and adjusted odds-ratios for this difference in patients with aneurysms versus patients with atherosclerotic disease were statistically significant," say the researchers.

They point out that animal studies show that disturbances in copper metabolism are associated with being prone to the development of aneurysms. "Preliminary studies have suggested that human beings with aneurysms may also have abnormalities of copper metabolism," the researchers say.

Tissue copper levels may be involved in the initiation and spread of cancer, the researchers report. "Copper has also been implicated in the functioning of the immune system," they add, pointing out that animal studies show that reduced white-cell activity is associated with being prone to aneurysms.

Another possibility is that the mutation linked to development of aneurysms might itself be cancer causing. "If the relationship between aneurysmal disease and oncogenesis suggested by the present data can be confirmed in larger and more comprehensive studies, it is possible that the association may reflect disturbed interactions between matrix proteins and epithelial cells of considerable biologic significance," the researchers conclude.

ASBESTOS FIBERS NOT AS UBIQUITOUS AS THOUGHT

The presence of asbestos in the lungs of the general population may not be as common as previously reported, according to a study in the July 6 issue of JAMA.

Ronald F. Dodson, PhD, of the University of Texas Health Center at Tyler, and colleagues compared autopsy specimens from three groups: 18 urban (Houston) residents who were thought not to be exposed to asbestos in the workplace and did not have lung cancer, 11 nonurban residents who were thought not to be exposed to asbestos at work but had lung cancer, and 12 former employees of a Tyler asbestos plant. Findings showed the number of coated asbestos fibers in specimens from the first two groups was generally low or below limits of detectability. The few exceptions were persons later found to have had an occupational exposure.

Among the occupationally exposed group, the coated asbestos fiber or "ferruginous body" content varied considerably between workers and also between sites in the same individual. Ten of the workers had cancer, and eight of these had lung cancer, the researchers report. All 12 workers had a history of smoking.

The findings that persons from other groups had few or no ferruginous bodies in their lungs differs from results of earlier studies of urban residents, researchers say. They suggest this may be because of the low background asbestos content in Houston.

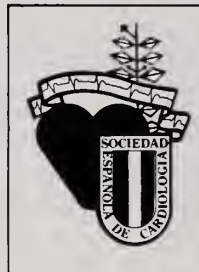
A contrary finding, however, is reported in the Journal by Alf Fischbein, MD, and Arthur N. Rohl, PhD, of the Mt. Sinai Medical Center in New York. They describe the case of a man who developed malignant pleural mesothelioma as a result of working next to a major navy yard from 1957 to 1966. He died of the disease in 1980. Amosite asbestos fibers found in the patient's lung tissue supported this causal relationship.

"Widespread use and occupational exposure to asbestos in US shipyards, particularly during World War II, is one reason for the currently high incidence of asbestos-related diseases, including lung cancer and mesothelioma," the researchers say. They add, "There is typically a long latency period between asbestos exposure and resulting disease."

A "Landmark" article by Irving J. Selikoff, MD, and colleagues of the Mt. Sinai Hospital in New York, first published in the April 6, 1964, issue of JAMA, describes a study of 632 insulation workers who entered the trade before 1943 and were traced through 1962. Forty-five of them died of cancer of the lung or pleura, whereas only 6.6 such deaths were expected, the researchers noted. "Four mesotheliomas in a total of 225 deaths is an exceedingly high incidence of such a rare tumor. In addition, an unexpectedly large number of men died of cancer of the stomach, colon or rectum," they said.

Commenting on the Selikoff study in a "Landmark Perspective," William R. Barclay, MD, editor emeritus of JAMA from Hilton Head, South Carolina, observes

"This article is a landmark in the medical literature because it established without any doubt that asbestos is a carcinogen, and it became the basis on which even stricter exposure limits were set for asbestos."



LA SECCION DE CARDIOLOGIA DE LA AMPR LA SOCIEDAD PUERTORRIQUEÑA DE CARDIOLOGIA INVITAN AL:

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Domingo 11 de noviembre de 1984

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Centro Especial Ramón y Cajal
Madrid, España

Dr. Bernardo Nadal-Ginard
Jefe, Cardiología Pediátrica
Boston Children Hospital
Boston, Massachusetts

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758-9459, 765-3595

What can you do for hypertensives like these?

On cimetidine

Impotent

Childhood
asthmatic

CNS
problems

Heavy
smoker

Diabetic

Patient descriptions are hypothetical composites based on clinical experience and evaluation of data.

Rely on one-tablet-a-day for these and virtually

Laura K is depressed... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN® (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma.¹ Smoking has been implicated—especially in males.² Cardioselective TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This preference is not absolute.

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence.

Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³

At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.⁴

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen.

Unlike propranolol, cardioselective TENORMIN can reduce the likelihood of bronchospasm in susceptible patients.^{5,6}



dosage and cardioselectivity* all your hypertensives.

newly diagnosed...
workup shows
62/100 mmHg. On
cimetidine for pep-
tic ulcer. Don S
states the thought
of yet another
medication.

TENORMIN is not
metabolized by the
liver. Its pharmaco-
kinetics are unaf-
fected when it is
administered con-
comitantly with
cimetidine^{7,8} or
ranitidine.⁹



"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹⁰



*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary of prescribing information.



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN[®] (atenolol)

Therapy
for virtually every
hypertensive
patient in your
practice.



TENORMIN[®] (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN[®] (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg./ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg./ml at 25 °C) and less soluble in chloroform (3 mg./ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. It dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyroidosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages, first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.5%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Medicolegal Decisions



PHYSICIAN HAS DUTY TO ADVISE PATIENT OF ALTERNATIVE FORMS OF TREATMENT

In obtaining a patient's informed consent, a physician must disclose alternative forms of treatment, including ones more hazardous than the recommended treatment, the Connecticut Supreme Court ruled.

A patient with systemic lupus erythematosus underwent a kidney biopsy to determine the extent of lupus involvement in her kidneys. Before performing the procedure, the urologist discussed it with her and told her that there might be some bleeding and a risk of hemorrhaging and of losing a kidney. The alternative of an open biopsy procedure under a general anesthetic was not mentioned. He did not consider it as a viable alternative because of a greater risk of complications. The patient signed a consent form after his discussion of the procedure with her.

During the biopsy, on November 3, 1972, the physician punctured the patient's gallbladder. It was later removed. The patient filed suit against the urologist for failure to obtain her informed consent. A trial court entered judgment for the physician, and the patient appealed.

Ordering a new trial, the Supreme Court said that a physician has a duty to advise the patient of possible alternatives in obtaining informed consent. The trial court committed reversible error in instructing the jury that the physician did not have to advise the patient of more hazardous alternatives to the proposed treatment. One expert witness testified that an open biopsy was a viable alternative to a closed needle biopsy. That was sufficient to present a jury question on the issue, the court said. The jury might have concluded that the urologist failed to furnish the patient with information she would have found material in making her decision on the course of therapy, the court said. In addition, the court stated that it was now aligning itself with order jurisdictions that had abandoned geographical restrictions for evaluating the standard of care in medical malpractice cases. —*Longan v. Greenwich Hospital Association*, 465 A.2d 294 (Conn.Sup.Ct., Sept. 6, 1983)

SURGEON LIABLE FOR BATTERY FOR PERFORMING HYSTERECTOMY WITHOUT PATIENT'S CONSENT

A surgeon was liable for battery for performing a total hysterectomy without the patient's consent, the Louisiana Supreme Court ruled.

The 27-year-old unmarried patient consulted the physician for complaints of lower abdominal pain that became so severe during her periods that she was unable to walk. He diagnosed a potential adnexal cyst or an endometrioma, in either case complicated by pelvic inflammatory disease. The patient obtained a second opinion that the pain was caused by pelvic inflammatory disease and endometriosis. She returned to the first physician, who performed a laparoscopy. He then proposed exploratory surgery to remove adhesions and the endometrioma. The patients signed a consent to a laparotomy.

During surgery, the physician found that her reproductive organs were so distorted by adhesions that he felt that she was already sterile. After consulting with the assisting surgeon, he performed a total hysterectomy and bilateral salpingo-oophorectomy. The patient became very upset when she learned that a total hysterectomy had been performed. When she refused to pay her surgical bill, the physician filed suit to collect it. The patient claimed malpractice and battery. A trial court and an appellate court found the physician not liable for malpractice and battery.

Reversing the decision, the Supreme Court said the evidence presented no reasonable basis for finding that the patient consented either expressly or impliedly to removal of her reproductive organs. The procedure was not forced by a lifethreatening situation, the court said. Although the procedure was performed skillfully and without negligence, the physician was liable for battery. The physician was not liable for damages for negligence.

The court remanded the case to the trial court for a determination of the damages due her for the battery. —*Karl J. Pizzalotto, M.D., Ltd. v. Wilson*, 437 So.2d 859 (La.Sup.Ct., Sept. 2 1983; rehearing denied, Oct. 7, 1983)

PEDIATRICIAN WINS INFORMED CONSENT SUIT

A pediatrician was entitled to summary judgment in an action for lack of informed consent, an Illinois appellate court ruled.

The patient entered a hospital for cesarean delivery of a

child. The pediatrician was in the operating room to receive the baby. The baby was in good health, except for a cleft palate. The obstetrician asked the pediatrician to speak with the patient's husband to determine if the husband wanted him to proceed with the sterilization procedure he had discussed with them three days before the delivery.

The husband was extremely upset when he learned of the child's condition and could not decide what to do. The obstetrician told the pediatrician to bring him to the operating room so he could talk with him. After talking to the obstetrician, the husband consented to the sterilization of his wife. A few days after the baby was delivered, congestive heart failure developed and the baby died within six weeks.

In a malpractice action against the two physicians, the trial court granted summary judgment in favor of the pediatrician. The patient appealed the decision, but the appellate court affirmed it. The pediatrician was not obligated to obtain an informed consent to the tubal ligation, and he did not voluntarily assume any duty to obtain an informed consent, the court said. He was unaware that the sterilization decision was based on the baby's being healthy. Any failure on the part of the pediatrician to obtain informed consent was not the cause of the patient's injury, the court said.—*Nichelson v. Curtis*, 452 N.E.2d 883 (Ill.App.Ct., Aug. 10, 1983)

PATIENT SUES FOR NERVE INJURY FROM NECK BIOPSY

A directed verdict was improper where evidence presented a question as to whether the risk of nerve injury could influence a reasonable person in deciding whether to undergo a lymph node biopsy, the Texas Supreme Court ruled.

In 1979, a patient consulted a surgeon after finding lumps in her neck. The surgeon recommended a lymph node biopsy, and the patient consented. The surgeon did not inform the patient that the procedure might traumatize the accessory nerve in her neck.

Soon after the surgery, the patient began to have impairment of the functions to her right shoulder and arm. When she discovered that her problems were caused by accessory nerve damage, she sued the surgeon, claiming that his failure to inform her of the risk prevented her from giving her informed consent to the surgery.

The only expert testimony offered by the patient was that of an otolaryngologist who practiced in another city. He stated that he was not familiar with the standard of care expected of physicians performing lymph node biopsies in the city where the operation took place or a similar community.

The trial court, relying on the locality rule, struck in testimony from the record and directed a verdict for the surgeon. An appellate court affirmed.

On appeal, the state supreme court said that in 1977 the Medical Liability and Insurance Improvement Act was enacted, replacing the locality rule with a "reasonable

person" rule. This rule focused on the disclosures that would influence a reasonable person in deciding whether to consent to a recommended medical procedure.

The Act created a medical disclosure panel, which was required to evaluate medical and surgical procedures and determine whether disclosure was required and, if so, how much. The panel had not evaluated and published a determination of the type of disclosure required in lymph node biopsies at the time of the patient's surgery. In such case, the Act provided that a physician was under a duty otherwise imposed by law. The court found the duty was to disclose all risks or hazards that could influence a reasonable person in deciding to consent to a procedure.

The Supreme Court said that the patient must prove by expert testimony that her problem was a risk inherent in the biopsy. The patient's expert had testified that the accessory nerve could be cut or traumatized by the manipulation necessary to free the lymph nodes. The court reversed the lower court's judgment and sent the case back to the trial court.—*Peterson v. Shields*, 652 S.W.2d 929 (Tex.Sup.Ct., May 18, 1983; rehearing denied, July 20, 1983)

PHYSICIAN NOT NEGLIGENT IN LYMPH NODE SURGERY

A physician was not negligent in operating on a patient to remove a lymph node in her neck, a Georgia appellate court ruled.

In early 1980, the patient consulted the physician concerning a tender and irritated lymph node in her neck. On June 11, he surgically removed the node. Immediately after the surgery, the patient began to experience weakness in her left arm, tingling sensations in her fingers, pain in the back of her neck and shoulder, and difficulty using her left arm. She had limited use of her left shoulder and arm and could no longer raise her arm above the shoulder. She went to a second physician. He diagnosed her condition as a left spinal accessory nerve lesion, probably caused by the prior surgery.

A trial court granted summary judgment for the operating physician and the appellate court affirmed. The patient's expert witness, a neurosurgeon, testified that injury to the nerve was a known risk of surgery. The fact that the nerve was injured was not evidence of negligence, the court said. Georgia did not follow the doctrine of informed consent, and the patient could not recover from the physician for negligence in failing to warn her of the possible risks of surgery, the court said.—*Simpson v. Dickson*, 306 S.E.2d 404 (Ga.Ct. of App., July 7, 1983)

RADIOLOGIST DID NOT HAVE DUTY TO REVEAL ALL RISKS

Under the informed consent doctrine, a radiologist did not have a duty to reveal all possible risks but only those material to a patient's decision on whether to undergo treatment, the Washington Supreme Court ruled.

The patient contacted her physician because of possible kidney problems. He referred her to the radiologist, who was to administer an intravenous pyelogram and take X-rays of her kidneys and ureters. Before administering the IVP, the radiologist informed the patient that her body might become flushed and that she might become nauseous and unconscious. He did not mention the ten other risks associated with the contrast agent mentioned in the *Physician's Desk Reference*, including thrombophlebitis.

As the radiologist began the procedure, the patient began to sneeze and suffered a shooting pain down her arm. Unaware of the pain, the radiologist completed the procedure and took X-rays. The pain persisted, and a week after the IVP, the patient's physician diagnosed reactive phlebitis. The patient's pain continued, and she had two related operations. Specialists diagnosed damage to the nerves in the patient's arm, but the record did not show whether the damage was related to the physician's diagnosis of phlebitis.

The patient sued the radiologist, alleging, among other things, failure to obtain her informed consent. At the trial the court rejected this claim. Although the court knew that the radiologist had not informed the patient of all risks described in the *PDR*, it concluded that she had not proved that any of them were medically significant or recognized risks or produced sufficient expert testimony on the issue. The court decided for the radiologist.

On appeal, the patient contended that the trial court erred in applying an incorrect standard in determining the risks that must be disclosed for a fully informed consent. The court said that under the informed consent doctrine a physician does not have a duty to inform of all possible risks but only those of a serious nature. Determination of whether a risk was material required first learning the nature of the harm and the probability of its occurrence, which required expert testimony, and second, a decision as to whether the probability of the type of harm was a risk that a reasonable patient would consider in deciding on treatment, which did not require expert testimony. In the present case, witnesses testified that the likelihood of the undisclosed risks occurring was remote. The appellate court said that the small probabilities indicated in the statistical evidence presented compared very favorably with those in other cases where nondisclosure had been held justified. The court affirmed the lower court's judgment.—*Smith v. Shannon*, 666 P.2d 351 (Wash.Sup.Ct., June 30, 1983)

SURGEON WINS INFORMED CONSENT MALPRACTICE SUIT

A patient could not recover for failure to warn of the risk of a fistula forming after a hysterectomy in the absence of proof that she would have withheld consent had the risk been disclosed, the Louisiana Supreme Court ruled.

Before undergoing the hysterectomy, the patient signed two consent forms, neither of which gave details of the operation or related risks. A vesicovaginal fistula was

diagnosed by a urologist after the operation, and surgery was performed later to correct the problem.

The patient sued the surgeon who performed the hysterectomy, alleging that the applicable statute created a duty on the part of the physician to inform her of known risks and that failure to do this supported an action in negligence. She also alleged that his failure to meet with her for a preoperative conference to answer questions as to the procedures to be performed gave rise to an action in strict liability. The trial court dismissed the case, and the decision was affirmed on appeal.

The Supreme Court said that the disclosure required by law included loss of function of an organ. The court said that the trial court erred in not finding that the vesicovaginal fistula was loss of function of an organ. The court said that the function of the bladder was to act a reservoir for urine and a bladder that leaked no longer performed its function. Since the risk of loss of function of an organ was not disclosed, there was no consent under law.

The court said, however, that not only must the patient show that the undisclosed risk actually occurred, but she must also prove that if the risk had been disclosed she would not have consented to the treatment. The court pointed out that the chance of a fistula forming after such an operation was very small and that such a possibility, where the complication could be corrected, should not be a determinative factor to a reasonable person in the patient's position. Finding that the patient failed to meet the burden of proof as to causation, the court affirmed the lower court's judgment.—*LaCaze v. Collier*, 434 So.2d 1039 (La.Sup.Ct., June 17, 1983; concurring opinion, July 8, 1983)

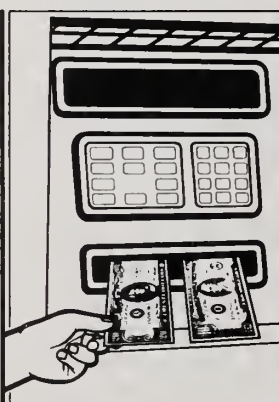
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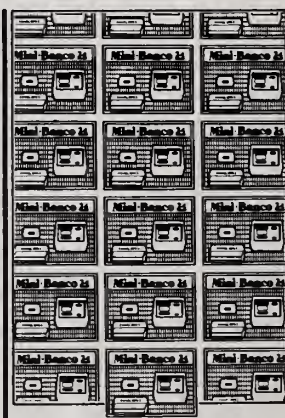
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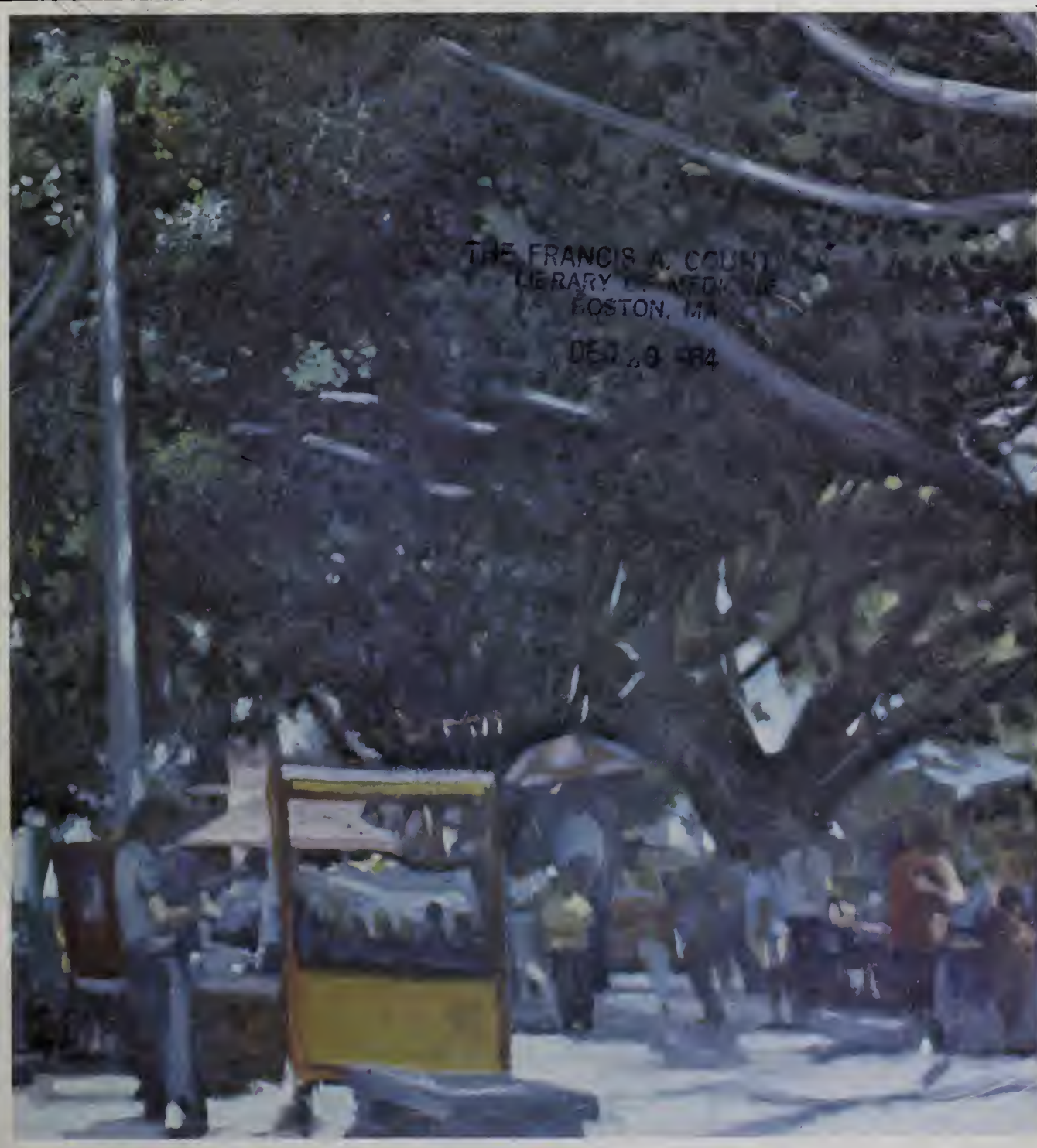
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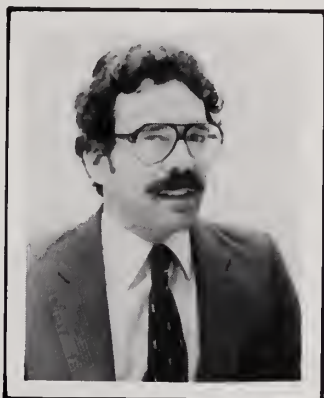
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Columna del Editor



A propósito del tema tratado en la pasada Columna del Editor quisiera hacer constar que se recibió correspondencia del Dr. Hernán Padilla donde contestaba las preguntas que la Junta Editora le hizo, al igual que a los demás candidatos a gobernador, con relación a los problemas de salud de Puerto Rico. Sin embargo fue enviada por correo 35 días después de la fecha límite señalada y ya el Boletín de octubre estaba impreso. Si se reciben contestaciones de los otros candidatos se publicarán en un suplemento del Boletín.

En este número aparece una sección nueva titulada Diagnóstico Angiocardiográfico. La misma es preparada por la Sección de Cardiología Pediátrica del Hospital Pediátrico Universitario y consta de angiocardigrafías donde se ilustran los hallazgos típicos de las diversas cardiopatías en niños. Todos los casos son del Laboratorio Cardiovascular de dicha institución, muchos de ellos referidos para estudio por pediatras de la comunidad. Esperamos poder ofrecerla regularmente y que sea de provecho académico para todos.

Rafael Villavicencio, MD, FACC
Presidente Junta Editora
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ASOCIACION MEDICA DE PUERTO RICO

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NUESTRA PORTADA

El Parque Muñoz-Rivera, Oleo del artista Rafael Tufiño. El autor nació en Nueva York, en 1922, de padres puertorriqueños. Empezó sus estudios en Puerto Rico con el maestro español Alejandro Sánchez Felipe. Con la ayuda de Juan Rosado, que presidía la American Artist Professional League, de Puerto Rico, se va a México y estudia en la Academia de San Carlos, bajo la dirección de Chávez Morado, Zalce, Castro Pacheco y Luna. También recibió clases en México, de Benjamín Coria, Ernesto Jorajuria, Dublán, Centeno y Pallares.

Al regresar a Puerto Rico, ingresó en la División de Educación de la Comunidad, y en el Centro de Arte Puertorriqueño. En 1956, recibió la beca Guggenheim y realizó la Serie del Café. Ha trabajado en la Escuela de Artes Plásticas del Instituto de Cultura y ha expuesto sus pinturas y grabados en varias salas de Puerto Rico. Participó en la Bienal de México, mientras que la Biblioteca del Congreso, de Washington, adquirió una obra suya, y la Reinhold Publishing Co. publicó uno de sus carteles en uno de sus anuarios, junto a importantes artistas de Europa y América.

Tufiño se crió en el área de Puerta de Tierra, por lo que conoce el parque desde su construcción. Era el lugar preferido por los artistas, sobretodo en la tranquilidad de la noche, para comentar sobre sus obras y preocupaciones comunes. Relata el autor que pasaba muchas horas en el parque, siendo una de sus favoritas las tardes del domingo, de las cuales guarda remembranzas especiales. Durante las horas laborables tampoco podía apartar el parque y mientras se desempeñaba como profesor de Artes Plásticas en el Instituto de Cultura Puertorriqueño lo utilizaba como salón de clases al aire libre.

Próximamente esta obra será reproducida en serigrafías para disfrute de todos. La reproducción de este óleo en nuestra portada ha sido posible gracias a la gentileza del autor y de los doctores Juan R. Colón Pagán y Filiberto Colón Rodríguez. La Junta Editora agradece esta colaboración con nuestra revista.

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ALUPENT SYRUP 10 mg/5 ml

Especially for children...pleasant cherry flavor, virtually no sugar or alcohol, no tartrazine

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Inhalant Solution

Bronchodilator

Please see following page for brief summary of the prescribing information, including warnings, precautions, and adverse reactions.

**When administered by IPPB

†In repetitive-dosing studies with Alupent Tablets and Alupent MDI, the duration of their effectiveness tended to diminish with time. Present studies are inadequate to explain the divergence in duration of efficacy between single and repetitive dosing.

References:

1. Reilly, EB *et al.* A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. *Curr Ther Res* 1974; 16: No. 8, 759-764.
2. Data on file at Boehringer Ingelheim Ltd



Alupent[®]

(metaproterenol sulfate)

Bronchodilator

Tablets
Metered Dose Inhaler
Syrup
Inhalant Solution

Alupent[®]
(metaproterenol sulfate)
Bronchodilator

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Metered Dose Inhaler
Syrup
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Contraindications: Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Alupent, brand of metaproterenol sulfate, has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose, the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose and 31 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent, brand of metaproterenol sulfate, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents.

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste.

Overdosage: The symptoms of overdosage are those of excessive beta adrenergic stimulation listed under **Adverse Reactions**. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

How Supplied: Round, white, scored tablets of 10 and 20 mg in bottles of 100. Metered Dose Inhaler containing 225 mg of metaproterenol sulfate (300 inhalations); 15 mg per ml (approximately 0.65 mg delivered with each metered dose). Cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 oz bottles. Inhalant Solution 5% in bottles of 10 ml with accompanying calibrated dropper.

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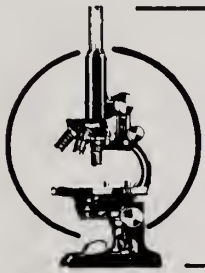
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PATHOLOGY *Review*

María Castillo Staab, M.D.*

Un hombre de 60 años con hipertensión arterial es hospitalizado quejándose de dolor abdominal persistente y dolor en la región lumbar. El examen físico reveló una masa abdominal en el área peri-umbilical y disminución de los pulsos femorales.

El segundo día de hospitalización el paciente desarrolló un cuadro de shock hipovolémico y falleció horas más tarde.

Los hallazgos en la autopsia son los que se demuestran en la fotografía a continuación:



¿Cuál es su diagnóstico?

- A) Aneurisma disecante de la aorta abdominal.
- B) Hemangiosarcoma de la aorta abdominal.
- C) Sarcoma de la vena cava inferior.
- D) Aneurisma sifilítico de la aorta abdominal.
- E) Aneurisma aterosclerótico de la aorta abdominal.

*Departamento de Patología, Universidad de Puerto Rico, Recinto de Ciencias Médicas, Río Piedras, Puerto Rico

ANEURISMA ATEROESCLEROTICO DE LA AORTA ABDOMINAL

Los aneurismas de la aorta abdominal son en su mayoría de origen ateroesclerótico. Ocurren en la porción distal de la aorta abdominal por debajo del origen de las arterias renales extendiéndose hasta la bifurcación y a veces al origen de las arterias ilíacas.

Estos aneurismas ocurren con mayor frecuencia en hombres después de los sesenta años de edad, son de tipo fusiforme y al momento de diagnosticarse usualmente han alcanzado un tamaño que excede 10 centímetros de diámetro.

Los aneurismas ateroescleróticos son el resultado de la debilidad de las capas elásticas y media de la pared de las arterias producidas por las placas ateromatosas y la fuerza circulatoria de la sangre.

La parte interna del aneurisma está compuesta de trombos frescos y organizados resultantes del enlentecimiento de la sangre en el espacio aneurismático. La mayoría de los aneurismas abdominales son clínicamente silenciosos pero pueden romperse, ocasionado sangramiento masivo dentro de la cavidad peritoneal y muerte por shock hipovolémico como sucedió con nuestro paciente.

Se calcula que uno de cada tres pacientes con aneurismas abdominales muere como resultado de esta complicación y el riesgo aumenta cuando el aneurisma mide más de seis centímetros de diámetro.

En ocasiones la ruptura conlleva una lenta pérdida de sangre y el paciente suele presentarse con dolor abdominal persistente, fiebre y evidencia de anemia moderada.

Otras complicaciones menos frecuentes son el desarrollo de una fistula aortovenosa por ruptura dentro de la vena cava inferior y hemorragia gastrointestinal por ruptura dentro del duodeno.

Las complicaciones no relacionadas con ruptura de los aneurismas abdominales usualmente dependen de fenómenos embólicos a las extremidades inferiores o de fenómenos de compresión a las estructuras antómicas adyacentes.

A través de la historia clínica y del examen físico se diagnostican el 80% de los aneurismas abdominales. Las técnicas de ultrasonido y de tomografía axial computarizada proveen incalculable ayuda para el diagnóstico y seguimiento de estos pacientes.

El manejo de los pacientes con aneurisma abdominal es esencialmente quirúrgico. La cirugía electiva envuelve el reemplazo de la porción aneurismática con un tubo de Dacron o de Gore-Tex.

La mortalidad de la cirugía electiva oscila entre 5 y 10%.

La cirugía obligada después de la ruptura conlleva una mortalidad de 70%.

Referencias

1. Hurst JW: The heart, arteries and veins 5th Ed., New York, McGraw-Hill 1982; p 1432.
2. Anderson WA: Pathology, 7th Ed., CV Mosby, St. Louis 1977; p 104.
3. Gore I, Hirst AE: Arteriosclerotic aneurysms of the abdominal aorta: a review. Prog Cardiovasc Dis 1973; 16:113.



LA SECCION DE CARDIOLOGIA DE LA AMPR LA SOCIEDAD PUERTORRIQUEÑA DE CARDIOLOGIA INVITAN AL:

Primer Intercambio Iberopuertorriqueño de Cardiología

Domingo 11 de noviembre de 1984

Lugar: Condado Holiday Inn

Profesores Invitados:

Dr. Antonio J. Bayés de Luna
Profesor de Cardiología de la
Facultad de Medicina
Universidad de Barcelona, España

Dr. Enrique Asín Cardiel
Servicio de Cardiología y Medicina Nuclear
Centro Especial Ramón y Cajal
Madrid, España

Dr. Bernardo Nadal-Ginard
Jefe, Cardiología Pediátrica
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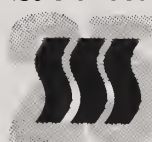
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What can you do for hypertensives like Don S?

New patient

Workup at 56 shows a systolic of 162 mmHg, diastolic of 100 mmHg.

Dislikes taking medication

Prior to last year, never sick in his life. Hates the thought of yet another medication.

Coexistent ulcer

Previous physician put him on cimetidine.

Loves food

But often eats on the run... vows to be more careful.



Patient description is a hypothetical composite based on clinical experience and evaluation of data

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Don S represents 899 black patients between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even in Don S's racial and age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Compatible with cimetidine and ranitidine

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when administered concomitantly with cimetidine or ranitidine.³⁻⁵ This compatibility of TENORMIN with today's widely prescribed H₂ receptor antagonists makes it a logical choice for hypertensives like Don S who are under treatment for a coexistent ulcer.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁶ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Don S...and virtually
all your hypertensive patients

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.



ONE TABLET A DAY TENORMIN® (atenolol)

For Don S...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-(1-methylethyl)amino]propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol:water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol) with caution—see OVERDOSAGE. Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacu-

lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methylglutamate.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on file, Stuart Pharmaceuticals. 2. Herman RL, Lamdin E, Fischetti JL, Ko HK. Postmarketing evaluation of atenolol (Tenormin®): A new cardioselective beta-blocker. *Curr Ther Res* 1983; 33(1):165-171. 3. Feely J, Wilkinson GR, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. *N Engl J Med* 1981; 304:692-695. 4. Kirch W, et al. Influence of beta-receptor antagonists on pharmacokinetics of cimetidine. *Drugs* 1983; 25(suppl 2):127-130. 5. Spahn H, et al. Influence of ranitidine on plasma metoprolol and atenolol concentrations. *Br Med J* 1983; 286:1546-1547. 6. Zacharias FJ. Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980; 6(suppl 1):86-89.



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Prognostic Value of Exercise Testing Early After Uncomplicated Myocardial Infarction

Esteban Linares, M.D., F.A.C.P., F.A.C.C.
Guillermo Cintrón, M.D., F.A.C.P., F.A.C.C.
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Summary: One hundred-thirty patients with uncomplicated myocardial infarction underwent submaximal treadmill exercise testing an average of three weeks after the index infarction. Forty seven patients (36%) had a positive response defined as the development of ≥ 1 mm ST-segment horizontal or downsloping depression with or without accompanied chest pain. Chest pain considered to represent angina pectoris without concomitant ischemic ST-segment depression was also considered a positive response. Thirty-five (75%) of the 47 positive responders developed angina pectoris during the subsequent year compared with 35 (42%) of the 83 patients with negative response ($p < .001$). There was no correlation between a positive response and re-infarction, aorto-coronary bypass surgery or cardiac death during one year follow-up. No complications were found as a result of the test in the study group.

Exercise testing early after uncomplicated myocardial infarction is performed in many centers nowadays in order to detect a high risk group of patients for the development of subsequent coronary events within a relatively low risk group. After the identification of such patients, more aggressive therapeutic modalities can be instituted. Also, early exercise testing give us an objective evaluation of the patient exercise tolerance and therefore guide us in the prescription of physical activities during the convalescent period.

The purpose of this article is to report our experience with three weeks treadmill exercise testing in 130 patients with uncomplicated myocardial infarction and to briefly review present concepts about pre-discharge exercise testing and its usefulness.

Material and Methods

This study covers the period between March 1979 to September 1980. One hundred-thirty patients with the proven clinical diagnosis of acute myocardial infarction and without any of the exclusion criteria noted on Table I were exercised following the Naughton protocol.¹ Patients were considered to have a Q-infarct if besides the typical pain in the chest and elevation of cardiac enzymes, new Q waves appeared. If only changes in the ST-T wave

TABLE I

Patient Selection

All Patients With Myocardial Infarction Except Those With:

1. Rest or unstable angina pectoris at the time of testing
2. Clinical congestive heart failure
3. An audible S_3 Gallop
4. Significant cardiac valvular disease
5. Hypertension greater than 180/100 mm Hg
6. Pulmonary disease
7. Musculoskeletal disorders exercise capacity
8. EKG evidence of LBBB or atrial fibrillation

were present, a non-Q wave infarct was diagnosed. The presence of major arrhythmia or pump failure occurring earlier in the hospital course did not exclude the patient if these abnormalities were absent at the time of hospital discharge. Each patient was interviewed and examined by a physician, and informed consent was obtained prior to the test, which was supervised by a physician and a specially trained exercise EKG technician. Twelve lead ECGs were recorded at rest, at the end of each 3-minute stage of exercise, and at 2, 4 and 6 minutes of recovery, unless the patient had significant ST segment depression in which tracings were taken every two minutes until return of the ST segment to baseline. Leads III, V_1 and V_5 were displayed continuously on a three channel oscillographic monitor and recorded during every minute of exercise. Blood pressure was checked manually before the beginning of the exercise and at the end of each stage of the Naughton protocol. Exercise was performed on a motor-driven treadmill using the protocol described by Naughton et al. Most patients started at Stage 3 (2 mph, 3.5% grade) or lower depending on the clinical estimate of their capacity. The work load was increased by one stage every third minute until attainment of an arbitrary "target" heart rate or 70% of age predicted maximum heart rate or work load of 4-5 METs whichever came first or the appearance of any of the following endpoints: 1) appearance of chest pain believed to represent angina pectoris in the opinion of the supervising physician, shortness of breath, fatigue, leg cramps or dizziness (symptom-limited tests), 2) staggering gait, a lack of increase or a fall in systolic blood pressure of at least 10 mm Hg below the peak value attained at a prior stage, or the appearance of ventricular tachycardia, i.e. three successive ventricular premature contractions or the development of marked ST segment depression (visual

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estimation of 2 mm horizontal or downsloping ST depression (sign limited tests).

An ischemic ST segment depression was defined as a horizontal or downsloping displacement of the ST segment of at least 0.1 mV below the baseline.

A negative responder was defined as a patient who did not develop chest pain or an ischemic ST depression as previously defined. A positive responder was defined as a patient who developed an ischemic ST depression or chest pain (with or without concomitant ischemic ST segment response).

Medical records were reviewed to determine the incidence of coronary events defined as the development of angina pectoris, myocardial infarction, the need for aorto-coronary bypass surgery and cardiac death in the subsequent year. Results were analyzed by the Chi square test.

Results

The mean age of the studied group of 130 patients was 55 years with a range from 40-72 years. One hundred fourteen (88%) had a Q-infarct, of which 48 (42%) were of anterior and 66 (58%) of inferior location. Sixteen (12%) had a non-Q infarct. Thirty patients (23%) had a previous myocardial infarction.

Indications to Stop the Test

Sixty seven (52%) of the group were able to achieve the pre-selected work load or heart rate. In fifty four (42%) the test was stopped because of the following: a) chest pain believed to represent angina pectoris in 25 patients (20% of the whole group), b) fatigue in 25 and, c) dizziness in 4. (See Table II) Eight patients (6%) developed electrocardiographic changes that were considered of enough severity to stop the test, five patients developed frequent PVC's and 3 patients marked ST depression. One patient was considered to have exertional hypotension (a lack of increase in his systolic blood pressure as the work load was increased). Eighty-three patients (64%) had a negative response and 47 (36%) a positive response.

TABLE II

Prognostic Value of Exercise Testing Three Weeks After Myocardial Infarction

N=130

Reasons to stop:

A. Achievement of pre-selected work load or heart rate	67 (52%)
B. Symptoms	54 (42%)
1. Angina Pectoris	25
2. Fatigue	25
3. Dizziness	4
C. ECG Changes	8 (6%)
1. Frequent PVC'S	5
2. Marked ST depression	3
D. Abnormal BP response	1

Correlations with Coronary Events

The correlation between the exercise test results (negative or positive response) and the development of angina pectoris during subsequent year can be seen in Table III. Negative responders (83 patients) had a 42% incidence of angina pectoris as compared with 75% of the positive responders, during a one year follow-up. This difference was statistically significant ($p < .001$).

TABLE III

Correlation Between Exercise Tests Results and Development of Angina Pectoris During One Year Follow-Up

N=130

	Angina Pectoris	
	Yes	No
1. Negative responders (N=83) No AP Nor ST ↓	35 (42%)	48 (58%)
2. Positive responders (N=47)	35 (75%)*	12 (25%)
ST ↓ Alone (N=17)	10	7
AP Alone (N=16)**	13	3
ST ↓ + AP (N=14)**	12	2

* $P < .001$

** $P < .05$

The correlation between exercise induced chest pain and the development of angina pectoris during the subsequent year can be seen in Table IV. Of 30 patients who had exercise induced angina pectoris, 25 (83%) had subsequent angina during the follow up period while 45 (45%) of the patients without such response developed angina in the subsequent year. This difference was statistically significant ($p < .001$). Stated in other way, 70 patients (54%) of the total group developed angina pectoris during the first year after the infarction. The development of angina pectoris during the test increased the probability of subsequent angina from 54% (without early testing) to 83%. In contrast, the absence of angina during the test, decreased the probability of developing angina pectoris from 54% to 45%. Sixty (46%) of the 130 patients studied with early exercise testing, had angina pectoris within 3 months prior to the index infarction. We found 17 patients who had both angina pectoris prior to the infarction and during the test; 15 of them (88%)

TABLE IV

Correlation Between Exercise Induced Chest Pain and Development of Angina Pectoris During One Year Follow-Up

N=130

	Angina Pectoris	
	Yes	No
Exercise-Induced Angina (N=30)	25 (83%)*	5 (17%)
No Exercise-Induced Angina (N=100)	45 (45%)	55 (55%)

* $P < .001$

developed angina during the subsequent years. In contrast, of 50 patients who neither had angina pectoris prior to the infarction or during the test, only 19 patients (38%) developed angina during the first year follow up period ($p < .001$).

As can be seen from Table V, no correlation was found between positive response to early exercise testing and the subsequent development of re-infarction, the need for aorto-coronary bypass surgery or sudden death.

No complications were noted in the group tested.

TABLE V

Correlation Between Exercise Test Results and Coronary Events During One Year Follow-Up				
N=130				
Coronary events N=19	Negative responders N=83	Positive responders N=47		
		ST ↓	AP	AP+ST ↓
None (N=111)	74	13	14	10
Myocardial infarction (N=9)	5	2*	0	2
Aorto coronary bypass surgery (N=8)	3	2	2	1
Sudden death (N=2)	1	0	0	1

*One patient suffered sudden death 2 1/2 months after MI

Discussion

Motivated by reports of European investigators^{2,3,4} in the early 70's regarding the safety of submaximal as well as symptom-limited exercise testing three weeks after an acute myocardial infarction, we began to perform early exercise testing (mean 3 weeks after the index infarction) in March, 1975. The main objectives to perform the test were to quantitate an estimated functional capacity in order to provide us an objective guideline for the recommendation of physical activities during the convalescent period (from 3 to 12 weeks after the infarction). Most of the patients had a submaximal exercise test at 6 weeks to determine the prescription for new levels of physical activity and another one, at 12 weeks, usually a symptom-limited test. Other objectives of the test were to detect latent myocardial ischemia or ventricular arrhythmias and to evaluate the significance of exercise test abnormal responses in relation to the development of future coronary events (prognostic value of the test).

It appears that the safety and feasibility of modified treadmill exercise testing before hospital discharge in selected patients (see Table I) after myocardial infarction has been adequately demonstrated.¹⁻⁹ Theroux and Waters reported only three complications (ventricular

tachycardia) in over 2000 tests performed.¹⁰ It should be clarified that the demonstrated safety has occurred when the test is performed under ideal circumstances. There are some anecdotal reports of mortality and morbidity from such testing. This is not a test to be performed outside the hospital setting or to be monitored by those who do only occasional exercise testing. The safety of the test relates more to patient selection (absence of unstable angina, clinical congestive heart failure or uncontrolled arrhythmias at the time of testing) than to the protocol used (submaximal or symptom-limited). We have been performing symptom-limited test in this group of patients without complications since 1980.

In our study, a positive response (an ischemic ST segment depression or the development of angina pectoris) failed to correlate with the development of future coronary events such as unstable angina pectoris or reinfarction.^{5,6}

We found, as well as others,^{11,12} that exercise induced angina pectoris (with or without ST segment depression) is predictive of subsequent development of angina, but not of outcome, in agreement with Weld's report.¹³ In contrast, Schartz et al¹⁴ reported that the mortality rate during a 2 year period was 46% in the presence of post-myocardial infarction angina, compared with 3% in its absence. However, the presence of angina was not an independent predictor, most of the patients with angina simultaneously showed a low tolerance to exercise or concomitant ST-segment depression both of which have been associated with increased mortality.^{5,6,7,11,12,13,15}

The lack of correlation between a positive response (ischemic ST-segment depression or the development of chest pain) and reinfarction in our study is in agreement with other studies,^{7,11,13} but in discordance with the study of Smith et al.⁶

It should be realized that the prognostic value of various parameters may also be influenced by the characteristic of the populations studied. This may explain some of the reported differences where different variables were studied in different populations. Our studied population had a low incident of cardiac death (1.5%), therefore, we can not reach any conclusion regarding the value of a positive response and subsequent cardiac death with the number of patients studied. In most of the reported series the risk appears to be doubled.

Clinical Usefulness

A number of factors predict mortality following myocardial infarction, mainly residual ischemia, left ventricular function, electrical instability and extent of coronary atherosclerosis. It has been shown that prognosis during the first year appears to be related to myocardial ischemia and the two to five year prognosis appears to be influenced mainly by left ventricular function. A pre-discharge exercise test, usually done between the seventh to fourteenth day after an "uncomplicated" myocardial infarction is an excellent complement to the clinical evaluation and provides us with information on various aspects of cardiovascular function, which is useful to assess prognosis, orient further investigations, and institute treatment. Also, its

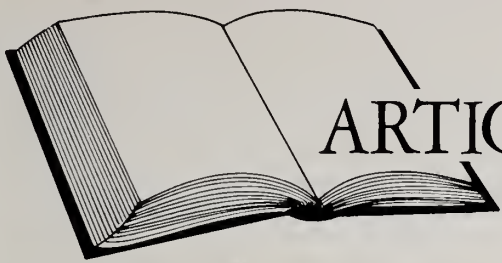
value to advise patients about physical activity after discharge might alone justify its use.¹⁶ We have been given advice in relation to sexual activity according to test results. Patients with negative response at work loads of 5 or more METs and at heart rates greater than 120-130 beats per minute do not need to have their sexual activity limited.¹⁷ Also, we believe that patients with negative response to pre-discharge testing should not be given secondary prophylaxis with betablockers as this is a very low risk group with an expected annual mortality of 1-2%. Patients who developed chest pain during the test, are either started on antianginal therapy or their medication is optimized prior to discharge. Only patients who remained symptomatic in spite of adequate medical treatment are referred for coronary angiography to evaluate the possibility of coronary bypass surgery. Patients with asymptomatic ischemic ST-segment depression are scheduled for thallium stress test as is some series.¹⁸ Up to one third of this patients had a negative thallium stress test, therefore, the ST-segment depression does not represent myocardial ischemia in such patients. In summary, in a convalescent acute myocardial population without contraindications to testing or limiting musculo-skeletal conditions will benefit (an estimated 60%) from an exercise evaluation for noninvasive assessment of functional cardiac status and risk for post-hospital cardiac death.

Resumen: Ciento treinta pacientes con infarto agudo de miocardio no complicado fueron sometidos a prueba submáxima de esfuerzo en la polea sin fin un promedio de tres semanas después del infarto índice. Cuarenta y siete pacientes (36%) tuvieron una respuesta positiva, definida como el desarrollo de una depresión del segmento ST > 1 mm de configuración horizontal o cuesta abajo con o sin dolor de pecho concomitantemente. El dolor de pecho considerado como angina de pecho, sin cambios isquémicos del segmento ST concomitante, fue considerado también una prueba positiva. Treinta y cinco (75%) de los 47 pacientes con prueba positiva desarrollaron angina de pecho durante el año subsiguiente a la prueba, comparado con 35 (42%) de los 83 pacientes con respuesta negativa ($p < .001$). No se encontró correlación entre una prueba positiva y el desarrollo un año después de reinfarctos, cirugía de puente aorto-coronario o muerte cardíaca. No hubo complicaciones como consecuencia de la prueba de esfuerzo en el grupo estudiado.

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ARTICULOS DE REPASO

Lyme Disease: A Review

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Abstract: Lyme disease is an immune-mediated inflammatory disorder which typically begins in summer with a characteristic skin lesion, erythema chronicum migrans, and is frequently accompanied by malaise, fatigue, fever, stiff neck and headaches. This is sometimes followed within weeks to months by nervous system, heart or joint involvement. The propensity to develop lyme disease seems to be associated with the B-cell alloantigen DRw2. Recently, the causative agent has been identified as a spirochete transmitted by the minute tick *Ixodes dammini*. Neurologic and cardiac abnormalities are found in 14% and 87% of the cases, respectively. Arthritis is more common and typically recurrent in contrast to the neurologic and cardiac abnormalities which rarely recur. Almost all patients have evidence of circulating immune complexes (abnormal Clq-binding activity) which persist in those with neurologic or cardiac involvement. Recent studies suggest that the use of penicillin shortens the duration of erythema chronicum migrans and may prevent or attenuate subsequent arthritis. Nevertheless, the neurologic or cardiac abnormalities frequency is similar regardless of treatment. The recommended treatment is oral penicillin G 250,000 units four times a day for 7-10 days or tetracycline 250 mg four times a day for the same period.

Lyme disease is an epidemic, immune-mediated inflammatory disorder that has its peak incidence during the summer. This "new" form of arthritis begins with a characteristic skin lesion, erythema chronicum migrans, and may be followed weeks to months later by neurologic or cardiac abnormalities, migratory polyarthritis, intermittent attacks of oligoarticular arthritis,

or "chronic arthritis in knees".¹⁻⁵ The geographic distribution of this disease in the U.S.A. supports previous epidemiologic evidence for transmission by a tick vector. The tick was saved from six patients and was identified as nymphal *Ixodes dammini*. The disease seems to occur in three distinct foci: along the northeastern coast, in Wisconsin, California, and Oregon, a distribution that correlates with that of *Ixodes dammini* in the first two areas and with *Ixodes pacificus* in the last.⁶ However, it has been reported in Europe⁷ and Australia.⁸

The earliest case known had its onset in Lyme, Connecticut in 1965, and from this town the disease took its name.

Etiology

Until recently it has been postulated that the *I. dammini* ticks transmitted a non-pyogenic penicillin-sensitive bacterium such as a spirochete.⁹ This was not confirmed until 1982 when a newly discovered spirochete was isolated from an adult *I. dammini* ticks in an endemic area for lyme disease.¹⁰ In 1983, Steere et al recovered the organism from the blood, the periphery of erythema chronicum migrans lesion and the cerebrospinal fluid, in three patients and correlated the clinical course with antibody response.¹¹

Similar finding by Benach et al had isolated also the *I. dammini* spirochete from the blood of two patients with lyme disease.¹²

It appears that the tick transmits the spirochete at the site where the skin lesion forms 3 to 20 days later. Somehow, the organisms reach the brain, heart and other organs, possibly hematogenously.

Clinical Features

Clinical onset is often marked by the appearance of an expanding skin lesion, erythema chronicum migrans, that follows the tick bite within 3 to 21 days and precedes the first attack of arthritis by weeks or months. The skin lesion typically lasts about 1 to 3 weeks, beginning as a red macule or papule that expands to form a large ring

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with central clearing. Associated symptoms ranged from none to malaise, fatigue, chills and fever, headache, stiff neck, backache, myalgias, nausea, vomiting, and sore throat. This phase lasts 2 to 3 weeks but rarely persists past 2 months. Attacks of arthritis occur as early as 1 week and as late as 14 months after the appearance of erythema chronicum migrans (ECM). This arthritis is typically episodic and confined to few joints, but may be migratory affecting both large and small joints.¹³ In some patients knee involvement becomes chronic and has progressed to pannus formation and erosion of bone and cartilage. Neurologic or cardiac involvement occurs within 1 to 10 weeks of the onset of erythema chronicum migrans. The neurologic abnormalities are found in 14% of patients and include: aseptic meningitis, encephalitis, cranial neuritis, motor or sensory radiculoneuritis, chorea, cerebellar ataxia, mononeuritis multiple, and myelitis. The usual pattern has been meningoencephalitis with superimposed cranial or peripheral neuritis. Cerebrospinal fluid pleocytosis and abnormal EEG have been observed in patients with the clinical picture of meningoencephalitis.¹³

Cardiac abnormalities are found in 87% of patients with lyme disease and include varying degrees of atrio-ventricular block (first degree to complete block) and right and left bundle branch block. Some patients present EKG changes compatible with acute myopericarditis, radionuclide evidence of mild left ventricular dysfunction or frank cardiomegaly. Signs and symptoms include: syncope or dizziness, shortness of breath, substernal chest pain, palpitations, tachycardia or bradycardia, loud S3 gallops, mild hepatojugular reflux and pericardial friction rubs. These extra-articular complications usually reach maximal intensity soon after the onset of erythema chronicum migrans and resolve completely after 2 to 8 months. They are also more common in young men.⁴

Immunopathogenesis

It has been suggested that circulating immune complexes play an important role in immunopathogenesis of lyme disease. Circulating immune complexes, that are detected by means of ¹²⁵I-Clq binding, Clq solid phase or Raji-cell assays, can behave like antigen-antibody complexes. Observations that ECM is the initial clinical manifestation of an immune-mediated inflammatory reaction have lead to studies of Clq binding activity in lyme disease.^{14, 15}

In lyme arthritis, the synovium is like that as in rheumatoid arthritis, repleted with lymphocytes and plasma cells. These cells are capable of producing immunoglobulins locally. The concentration of polymorphonuclear lymphocytes in synovial fluid of patients with lyme arthritis has been closely correlated with the Clq binding activity.¹⁵ It has been postulated the antigen (s) involved is probably derived from, or cross reactive with the spirochete isolated in these patients. Since rheumatoid is not found in the complexes nor in the serum of those patients affected with lyme disease, the antigen (s) involved are not likely to be the Fc portion of IgG as in rheumatoid arthritis.⁵ In other words, the articular manifestations of the disease appears to be

associated with the localization of Clq binding activity in the joint synovium. In a prospective study of 78 patients with lyme arthritis, abnormal serum Clq binding activity was present at the initial onset of ECM in nearly all of the cases.¹⁴ It persisted in those patients with subsequent neurological or cardiac involvement. This binding activity usually disappeared within 3 months in patients who developed subsequent arthritis only. However, in the synovial fluid of affected joints, abnormal binding activity was uniformly present and always greater than in the serum.¹⁴

It appears that also cryoglobulins may have an important role in the immunopathogenesis of this condition.

Early in the disease, when ECM alone is present, 90% of the patients affected will have elevated IgM cryoglobulins ($\geq 1:128$) against the spirochete. Later, when there is involvement of the nervous system, heart or joints, 94% of the patients will have elevated titers of IgG cryoglobulins ($\geq 1:128$).¹⁶ Therefore, cryoglobulins determination provides strong supportive evidence for the diagnosis of lyme disease. However, since serologic testing is not generally available, the diagnosis must be made by the clinical findings in most of the cases.

Recently, an enzyme-linked immunosorbent assay (ELISA) has been developed for the determination of titers of specific IgM and IgG antibodies to the *I. dammini* spirochete.^{17, 18} The sensitivity and specificity of an indirect immunofluorescence assay (IFA) has been compared with the ELISA; the ELISA was more sensitive and specific than was immunofluorescence for lyme disease.¹⁸

Concluding, the mechanism of immunopathogenesis is still unknown, however, research concerning the antibody response to *I. dammini* spirochete components¹⁹ may help elucidate the immune response found in this disease.

Differential Diagnosis

Several other disease should be considered when one confronts a patients with arthritis, neurologic and/or cardiac abnormalities. Cardiac abnormalities of lyme disease have similarities with acute rheumatic fever, which may follow group A streptococcal pharyngitis. In acute rheumatic fever, Jones major clinical criteria include: carditis, migratory polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. In ARF, carditis affects primary children between ages 5 to 15 years and is frequently asymptomatic. Valvular involvement is the commonest cardiac manifestation of ARF; 8% develops congestive heart failure and 6% develops pericarditis. Twenty-five to fifty percent develops prolonged PR intervals, but complete heart block is unusual. In contrast, in lyme disease adult men were most frequently affected, complete heart block was common, myopericardial involvement tended to be milder and valves seem not to be affected. Arthritis may be similar in both disease. *Yersinia enterocolitica* infection may cause valvulitis with myopericarditis and polyarthritis. But diarrhea and abdominal pain are characteristic and cardiac conduction abnormalities are unusual.

Rocky Mountain spotted fever is a rickettsial disease

transmitted by a tick (*Dermacentro variabilis*), which may cause myocarditis but arthritis does not occur. Of the viruses we must consider the coxsackie A & B, ECHO type 6 and 8, adenovirus type 3, influenza A, hepatitis B, Epstein Barr, mumps, polio, and varicella, especially if the patient presents with myopericarditis. Unlike lyme disease, the cardiac manifestations in these patients are often the presenting sign or symptom.⁹

Laboratory findings in lyme disease include:

- a. increased erythrocyte sedimentation rate (ESR)
- b. increased serum IgM levels
- c. increased cryoglobulins containing IgM and sometimes IgG
- d. increased serum SGOT
- e. anemia
- f. negative serologic tests for other disease (eg. *Rickettsia conorii*, *Rickettsia mooseri*, *Rickettsia prowasekii*)

Treatment

When initially a spirochetal etiology was suspected Hoostrom gave penicillin to 16 patients with ECM and noted prompt resolution of the lesion.²⁰ In 1962 Degos and co-workers reported that some patients with ECM have positive microagglutination titers against *Rickettsia conorii*, *Rickettsia mooseri*, and *Rickettsia prowasekii*. Subsequent work has failed to substantiate this finding as well. This report led to tetracycline therapy for ECM.²¹

In 1980, Steere, Malawista, and co-workers⁹ reported a study of 113 patients with ECM treated with penicillin, erythromycin, tetracycline, or not treated at all. They found that ECM and associated symptoms resolved faster in patients given penicillin or tetracycline (median duration, 4 and 2 days, respectively), than in untreated patients (10 days). Erythromycin had no significant effect. Although the frequency of subsequent neurological and cardiac abnormalities was similar in all four groups, significantly fewer patients given penicillin developed arthritis than did untreated patients. Among 15 patients with arthritis who were followed for at least 29 months, the total duration of joint involvement was shorter in penicillin-treated patients (median, 4 weeks) than in untreated patients (17 weeks).

They conclude in their study that penicillin therapy shortens the duration of ECM and may prevent or attenuate subsequent arthritis. But neurological or cardiac abnormalities frequency is similar regardless of treatment.⁹

The recommended treatment is oral penicillin G 250,000 units q.i.d. (7-10 days) or tetracycline 250 mg q.i.d. for the same period of time, if allergic to penicillin except in children younger than 6 years old because of the risk of tooth discoloration.²² Prednisone should be considered in those patients with cardiac and neurologic manifestations of the disease.^{3, 4} The initial recommended dosage for adults is 40 to 60 mg per day and 20 mg in children. Prednisone is then tapered in increments of 5 to 10 mg per week. More rapid decreases in prednisone may cause recurrences of cardiac or neurologic disease in some patients. Meningeal symptoms tend to respond favorably with prednisone therapy.

However, encephalitis, cranial, nerve and radicular symptoms do not respond as well than without prednisone.³

Resumen: La enfermedad de "Lyme" es un desorden inflamatorio mediado por mecanismos inmunes. Esta enfermedad típicamente comienza en el verano con una lesión de piel característica, el "erythema chronicum migrans", y frecuentemente se acompaña de malestar general, fatiga, fiebre, rigidez de nuca y dolor de cabeza. El cuadro inicial puede ser seguido semanas a meses más tarde por involucramiento neurológico, cardíaco o articular. La propensión de desarrollar la enfermedad de "Lyme" parece estar asociado con la presencia del aloantígeno de células-B DRw2. Recientemente, su agente causante ha sido identificado como una espiroqueta transmitido por la garrapata *Ixodes dammini*. Se han identificado anomalías cardíacas y neurológicas en un 14% y 87% de los casos, respectivamente. Los ataques de artritis son más comunes contrastando con las anomalías y se caracterizan por su recurrencia neurológica y cardíaca. Casi todos los pacientes tienen evidencia de complejos inmunes circulantes (actividad de enlace de Clq anormal) los cuales persisten en aquellos pacientes con involucramiento neurológico o cardíaco. Estudios recientes sugieren que el uso de penicilina acorta la duración de "erythema chronicum migrans" y puede prevenir o atenuar el desarrollo de artritis. Sin embargo, la frecuencia de las anomalías neurológicas o cardíacas es similar aún en presencia de antibióticos. El tratamiento recomendado es penicilina G oral 250,000 unidades cuatro veces al día por 7-10 días o tetraciclina 250 mg cuatro veces al día por el mismo lapso de tiempo.

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SIRVIENDO AL PUEBLO Y A LA PROFESION MEDICA



ASOCIACION MEDICA DE PUERTO RICO



Foro de Medicina Nuclear

Bone Scan in Sickle Cell Disease

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Case Summary

A 13 years old Puerto Rican girl with history of sickle cell disease since the age of 5 years and recurrent episodes of vaso-occlusive and hemolytic crises, was admitted on January 6, 1984 with a one day history of acute pain in the upper and lower extremities. Physical examination on admission revealed an alert, well-oriented female in acute distress because of pain. Blood pressure was 140/80 mm Hg; pulse, 100/min; temperature 37° C. Heart auscultation revealed a grade II/VI systolic murmur at 4th left intercostal space. There was tenderness in both knees, with no swelling, erythema or increased temperature.

Pertinent laboratory data on admission included a hemoglobin of 8.8 g/dl; hematocrit 25.4%; leukocytes 23,900/cu mm with 1 stab, 75 segmented, 24 lymphocytes and 13 nucleated red blood cells. Repeated blood and urine cultures were negative. Erythrocyte sedimentation rate was 58 mm/hr.

Two days after admission the patient developed fever and broad spectrum antibiotics therapy with ancef and garamycin was added to her ongoing therapy with intravenous fluids and analgesics. In view of persistent pain and fever, X-rays of right and left knee were done on January 17, 1984 and they were reported negative.

Bone scan was done on January 20, 1983 (Figs. 1,2)

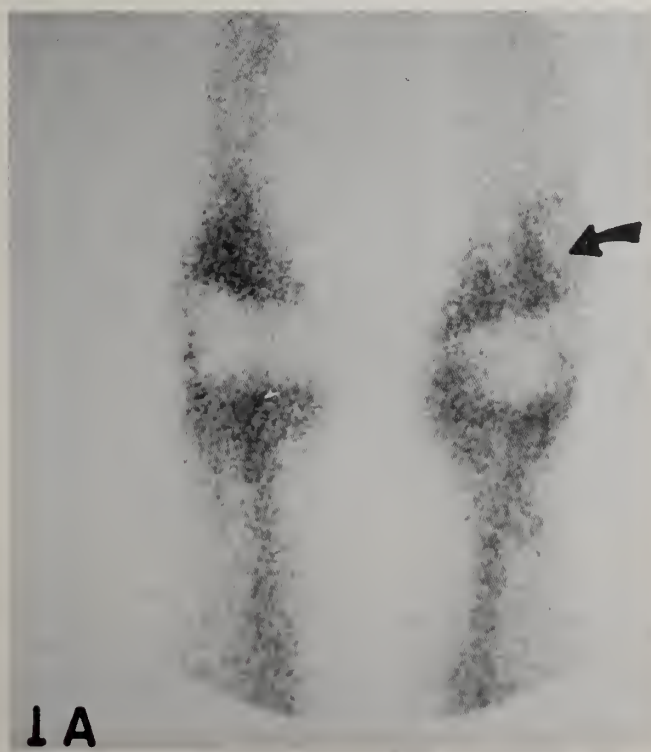


Figure 1-A

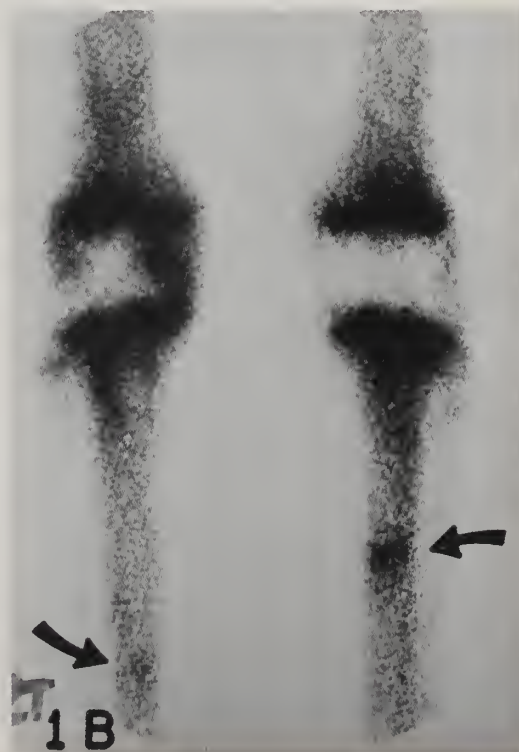


Figure 1-B

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Juan, Puerto Rico 00936

Figure 1: Early (A) and late (B) image of knees showed decreased activity on left knee (arrow) at the medial femoral condyle. There is focal increase activity (arrows) in both tibiae in the late image.



Figure 2: Bone scan (^{99m}Tc medronate) shows abnormal foci of tracer localization in both femurs (A), in left 9th posterior rib and in spleen (B), consistent with bone and spleen infarcts.

revealing abnormalities in the early and late images of the knees, both femora and tibia, ribs and spleen, consistent with bone infarcts. Antibiotics were discontinued after eleven days of therapy in view of blood culture results. The patient was discharged after twenty-one days afebrile, to continue with physical therapy.

Discussion

Bone infarct is a common complication of sickle cell disease due to the vascular sickling of erythrocytes. The most frequently affected bones are the humerus, tibia and femur.¹ Bacterial osteomyelitis is also frequently suspected in these patients although it is known that bone infarcts are 50 times more common than osteomyelitis.

The clinical picture of acute bone infarcts resembles that of acute osteomyelitis, and it is often difficult to distinguish one from the other. Laboratory evaluation including leukocyte counts, erythrocyte sedimentation rate, and roentgen evaluation in the early stages of disease, are not good discriminators. The long bone changes caused in X-rays by osteomyelitis and bone infarcts are similar. Periosteal elevation may be seen only after 10 to 14 days.¹ The most valuable tool in the diagnosis has been cultures of blood and material aspirated from the joint of bone.² With the availability of radionuclide bone imaging, a non invasive and simple method was introduced. Scintigraphy with bone localizing agents gives early indication of bone damage. Its reported sensitivity and specificity is over 90% in early osteomyelitis and bone infarcts.³

Bone infarcts within the first week of the onset of symptoms will show a photopenic area in the early and delayed images in the cases with vascular compromise while osteomyelitis presents as a "hot" lesion. Rarely osteomyelitis may present a "cold" lesion in bone scan on early studies. After about 7 days, when bone healing starts to be significant, the scintigraphic pattern changes to an area of increased activity in the affected bone, similar to the pattern seen in acute osteomyelitis. At this stage of disease, it is not possible to differentiate one entity from the other and whole body gallium scan is recommended.⁴ Gallium scan will become positive as early as 48 hours after the onset of infection, being then a good discriminator of infarct vs infection. In early bone infarcts, gallium imaging will be negative. Bone imaging in sickle disease will also depict areas of soft tissue infarcts, which may occur frequently in these patients, especially in lungs and spleen.

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ARTICULOS ESPECIALES

Pediatría del Desarrollo: La Nueva Pediatría Apuntes Sobre su Evolución

Nilda Candelario, M.D., F.A.A.P.

Bienaventurados los que comprenden mi extraño paso al caminar y mis manos torpes.

Bienaventurados los que comprenden que mis oídos tienen que esforzarse para comprender lo que oyen.

Bienaventurados los que comprenden que aunque mis ojos brillan, mi mente es lenta.

Bienaventurados los que con una sonrisa en los labios me estimulan a tratar una vez más.

Bienaventurados los que me respetan y me aman como soy; y no como ellos quisieran que yo fuera.

(Tomado de "Las Bienaventuranzas del Retrasado Mental"-Anónimo)

Desde que existe documentación de la Historia Humana, siempre ha habido personas "diferentes" cuyo desarrollo, por alguna razón, no ha sido normal. En los primeros textos de Pediatría como *The Booke of Children*, publicado en Inglaterra en 1545 se mencionan condiciones como "hinchazón de la cabeza" (hidrocefalia) y epilepsia (denominada en Inglés "Fallying Evil") sin indicar ningún tratamiento satisfactorio para ellas.

A través de los siglos, el interés de la medicina y luego de la nueva especialidad de pediatría estuvo enfocado al tratamiento y prevención de aquellas enfermedades que causaban estragos en la población infantil. Es por eso que se dirige el énfasis terapéutico e investigativo a la erradicación de enfermedades como tuberculosis, fiebre escarlatina, viruela y en años más recientes poliomielitis, entre otras. En los países civilizados y más industrializados, también se enfatizó la lucha contra el hambre y la malnutrición.

No es hasta principios del siglo 20, que el enfoque va lentamente cambiando hacia un interés en estudiar cómo se desarrollan los niños. El Doctor Arnold Gesell, fundador de la Clínica para el Desarrollo del Niño de la Universidad de Yale en 1911 es el primero en estudiar el desarrollo de los niños utilizando el método científico. El

abordaje del Dr. Gesell en los primeros años fue desde un punto de vista biológico y del estudio de patrones de conducta similar al del Dr. Sigmund Freud. La clínica del Dr. Gesell en Yale fue, sin embargo, el primer intento visible de un programa para estudiar el desarrollo integral del niño en lugar de separarlo en problemas de salud, necesidades educativas o problemas sociales y de comportamiento.

En el 1951 el American Board of Pediatrics reconoció la necesidad de expandir el currículo en el adiestramiento de pediatras para que incluyera mas información sobre el crecimiento y desarrollo del niño normal. El propio Dr. Gesell encomió esta acción de parte del American Board of Pediatrics pero les criticó que no fueran más específicos en relación al entrenamiento en lo que él llamó "aspectos especiales" del desarrollo de infantes y niños. Igualmente señaló que los pediatras tenían también que aprender sobre aquellos niños cuyo desarrollo no era normal y que tenían algún tipo de impedimento. Señaló el Dr. Gesell que la nueva definición de salud en el niño debería ser: "aquella condición que permite y promueve un desarrollo óptimo". Concluyó el Dr. Gesell en 1951 que "la demanda por un tipo de pediatría orientada hacia el desarrollo (Developmental Type of Pediatrics) está aumentando en volumen y penetración.

No es hasta la década de los 1960 que en los Estados Unidos hay un re-enfoque de la pediatría tradicional. En esta década se renueva el interés en la relación existente entre la salud y las condiciones socio-económicas, se demuestra la necesidad de enfocar problemas pediátricos desde una perspectiva multidisciplinaria y se enfatiza la importancia de programas para niños impedidos. A mediados de la década del 60 la Academia American de Pediatría en su informe "Standards of Child Health Care" reporta que el énfasis del cuidado pediátrico debe ser en "Pediatría Preventiva" y en manejar "Desórdenes emocionales y de Comportamiento". (AAP-1967)

En el 1979 el "Task Force on Pediatric Education" (compuesto de varias organizaciones envueltas con la educación médica en Pediatría) indicó que el área de pro-

blemas biosociales y de desarrollo, no había estado adecuadamente enfatizada en el adiestramiento de pediatras hasta entonces.

En la década de los 1970 hubo en los Estados Unidos una serie de cambios complejos en la actitud pública hacia aquellos ciudadanos (niños y adultos) cuyo desarrollo no era "normal". El énfasis inicial fue en personas con impedimentos físicos que habían sido hasta cierto punto marginados por la sociedad. Estos ciudadanos de momento se hicieron visibles y comenzó una intensa campaña en la que participaron activamente profesionales envueltos en el cuidado de estas personas con problemas de desarrollo. (Pediatras, Psicólogos, Psiquiatras, Terapistas, Educadores, Médicos Especialistas en diversos campos, etc.). Esta campaña culminó en legislación que por primera vez garantizaba a estos niños ciertos derechos inalienables que otros ciudadanos "normales" daban por descontados. La más conocida de estas leyes federales es la PL 94-142 pasada por el Congreso de los Estados Unidos en 1975 y llamada "The Education for all Handicapped Children's Act". La ley obliga a los estados a proveer "una educación pública compleja y apropiada" para todo niño con impedimento. La Ley aplica a niños con retardo mental, con impedimentos del habla, audición o visión, con impedimentos emocionales severos, con enfermedades crónicas y a niños con problemas específicos de aprendizaje. La sección 504, llamada "Ley de los Derechos Civiles de los Impedidos" estipula que se pueden eliminar los fondos federales a aquellos estados que no cumplan con las provisiones de la Ley 94-142.

Debido en parte a esta legislación los médicos se vieron directamente envueltos en el proceso de identificación de niños impedidos y su evaluación clínica. En muchas ocasiones se le pedía al médico su opinión sobre las necesidades de ese niño en la escuela. Es entonces que los programas de educación médica, respondiendo a esas nuevas necesidades, comienzan a integrar a sus currículos conceptos sobre las personas impedidas de una forma más organizada y eficiente. Los organismos acreditadores de programas de residencia enfatizan la inclusión de experiencias en el manejo de problemas; biosociales y de comportamiento, además de conocimientos en cuanto al desarrollo normal y a las disfunciones de desarrollo.

En la década de los 1970 la mayoría de los programas de residencia en pediatría y algunos programas de otras especialidades comienzan a ofrecer algún adiestramiento específico en problemas de desarrollo y comportamiento pero éste muchas veces es fragmentado.

En un estudio realizado por el Dr. P.H. Dworkin y asociados en 1979, el cincuenta por ciento de los pediatras entrevistados indicó que la educación pre-grado (Escuela de Medicina) no había sido de valor en proveer conocimientos sobre problemas de desarrollo. Veinte por ciento de esos pediatras indicaron que la residencia en pediatría tampoco les había brindado esos conocimientos. En otra encuesta realizada por el "Task Force on Pediatric Education" en 1978 entre siete mil pediatras recién graduados más del cincuenta por ciento indicaron que tenían experiencia insuficiente en el cuidado de niños con problemas psicosociales, de aprendizaje y de com-

portamiento. Más del cuarenta por ciento señalaron que su adiestramiento había sido deficiente en el cuidado de niños con retardo mental e impedimentos físicos.

Con toda esta información se hizo evidente que tanto las escuelas de medicina como los programas de residencia (tanto de pediatría, como de otras especialidades que brinden cuidado a niños impedidos, tales como: Neurología, Medicina de Familia, Ortopedia, Neurocirugía, etc.) tenían que proveer mayor experiencia en el manejo interdisciplinario y longitudinal de estos pacientes.

Debido a los avances en la medicina cada vez sobrevivían más niños con impedimentos que antes fallecían en el período neonatal o infancia temprana. El manejo de estos pacientes se fue haciendo más complejo y hasta cierto punto más fragmentado debido a la cantidad de especialista envueltos. Un ejemplo de esto es el infante con espina bífida el cual inicialmente es tratado por el neurocirujano y el pediatra, pero cuyo cuidado eventualmente envuelve Ortopedias, Nefrólogos, Urólogos, Neurológicos, Oftalmólogos, Terapistas Físicos y Ocupacionales, Patólogos del Habla, Psicólogos, Educadores Especiales y muchas veces Psiquiatras.

En el empeño de proveer alguien que sirviera de enlace y coordinara los servicios multidisciplinarios que requiere un niño impedido, se visualizó al Pediatra general primario como dicha persona. Sin embargo, se encontró que muchas veces el médico primario no tenía el tiempo ni el adiestramiento, y desgraciadamente a veces no tenía el interés de bregar con los problemas múltiples y complejos que presentan los niños impedidos y que requieren una gran inversión de tiempo y energía. Es entonces que se desarrolla en los Estados Unidos el concepto de "Developmental Pediatrician" (traducido literalmente como Pediatra especialista en desarrollo, a falta de una mejor traducción) y se establece programas de adiestramiento (Fellowship) en dicha disciplina.

El Pediatra especialista en desarrollo (Developmental Pediatrician) ha tenido la oportunidad de aumentar y profundizar los conocimientos y destrezas de evaluación y manejo de niños con impedimentos físicos, retardo mental, problemas de comportamiento y problemas de aprendizaje. Su adiestramiento le provee experiencia clínica extensa con un espectro variado de niños, tiempo para un seguimiento longitudinal prolongado y la oportunidad de laborar en conjunto con profesionales de otras disciplinas. Además, se le adiestra para ser maestro y compartir esos conocimientos con estudiantes, residentes y médicos de todas las especialidades. El pediatra especialista en desarrollo recibe adiestramiento en procedimientos gubernamentales y de Salud Pública y en la coordinación de servicios con diferentes agencias de la comunidad. Sobre todo, el pediatra especialista en desarrollo trabaja en forma transdisciplinaria con todos aquellos que de forma alguna se envuelven en el cuidado, rehabilitación y educación del niño con impedimentos.

El pediatra especialista en desarrollo (Developmental Pediatrician) tiene adiestramiento en campos como: Neurología, Psiquiatría, Ortopedia, Psicología y Educación Especial, pero no sustituye ninguno de estos profesionales. Por el contrario, estos son sus consultores y colaboradores más cercanos y figuras centrales en la prestación de cuidado integral al niño impedido.

Muchas veces el pediatra general o el médico de familia quiere seguir de cerca a sus pacientes impedidos. Esto es altamente encomiable y en esos casos el pediatra especialista en desarrollo podría servir una función de orientar y ayudar al médico primario en el cuidado de estos niños. Otras veces, el médico primario preferirá referir estos pacientes al pediatra de desarrollo quien asumirá entonces el rol del médico primario y coordinador de servicios.

La decisión de utilizar al pediatra de desarrollo como consultor o para referirle el paciente a su cuidado debe ser tomada por el médico primario en base de:

1. Sus conocimientos y experiencia y su disponibilidad para manejar problemas de desarrollo, comportamiento y/o aprendizaje.
2. Sus actitudes y filosofía personal en relación a los pacientes impedidos y sus familiares.
3. La situación física, emocional y económica de la familia.
4. La accesibilidad de los recursos de consultoría o tratamiento.

El médico primario es, sin embargo, el primer contacto del niño y su familia, el que sospecha a través del cernimiento temprano la presencia de alguna disfunción de desarrollo y el que, en virtud de su relación con la familia puede proveer el apoyo emocional inicial que es tan importante. Su rol inicial y en el cuidado continuado es vital para el niño impedido y para sus familiares.

A través de este recuento de la evolución de esta nueva rama de la pediatría, podemos concluir que ya la Pediatría del Desarrollo o "Developmental Pediatrics" ha llegado a su mayoría de edad. En los Estados Unidos se reconoce su importancia, particularmente en cuanto a la educación de médicos y otros profesionales de la salud y de la comunidad en general, y en cuanto a la prestación de servicios directos se refiere.

La gama de condiciones en las que se envuelve el pediatra especialista en desarrollo incluye entre otras:

1. Problemas de atención y/o de Hiperactividad.
2. Problemas de aprendizaje
3. Retrasos en desarrollo ("Developmental Delays")
4. Impedimentos Físicos (espina bífida, cerebral palsy, distrofias musculares, impedimentos de visión y audición, etc.)
5. Retardo Mental
6. Problemas menores de conducta y comportamiento (excluyendo problemas psiquiátricos)
7. Niños sobre-dotados
8. Disfunciones de desarrollo (Problemas motores, de percepción, etc.)
9. Problemas emocionales o escolares en niños con impedimentos físicos.
10. Problemas de comunicación y lenguaje.

En conclusión, la nueva rama de la pediatría está aquí... para quedarse. La Pediatría del Desarrollo ("Developmental Pediatrics") ha llegado a llenar un vacío en el cuidado de niños excepcionales y ha llegado a brindarles a los médicos de Puerto Rico una colaboración

y apoyo en la prestación de servicios a estos pacientes especiales y a sus familias.

Se ha recorrido un largo trecho en la evolución de este nuevo enfoque al cuidado del niño impedido. Esto hay que celebrarlo, pero falta aún mucho por recorrer para ayudar a estos niños a desarrollar su máximo potencial como seres humanos. Ese debe ser el compromiso moral, no sólo de la clase médica sino de todos los ciudadanos de Puerto Rico.

Resumen: Este artículo define lo que es el nuevo campo de Pediatría del Desarrollo (en Inglés, "Developmental Pediatrics") y la importancia que tiene en la prestación de cuidado longitudinal e integrar a niños con impedimentos físicos, problemas de comportamiento y problemas de aprendizaje. Se traza la evolución de esta subespecialidad que es la más nueva dentro de la Pediatría y se esboza su relación con el médico y con profesionales de la educación y de otras disciplinas aliadas a la salud. Además se discute la importancia de incluir la enseñanza de conceptos y destrezas relacionadas al niño con disfunción de desarrollo en los programas de educación médica pre y post graduada.

Abstract: This article describes the new field of Developmental Pediatrics and its importance in the delivery of longitudinal care to children with physical disabilities and behavior or learning problems. The evolution of the newest subspecialty within pediatrics is traced. Its relationship with physicians, other health professionals and educators is also described. Emphasis is placed on the importance of including skills and knowledge related to the child with developmental dysfunction in the medical school curriculum and in the residency training programs.

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Computers in the Medical Office: The Revolution Continues*

Peter C. Tolos, PhD**

Minicomputers costing almost \$100,000 began appearing in large clinics or multiple-physician practices some ten to 12 years ago. The programming needed to make these systems handle medical billing, insurance processing, and scheduling took years to develop, and costs were staggering. System inefficiency, program errors, and dependence on immature or incomplete systems sometimes reduced cash flow and crippled operations. There were successful systems, but high prices put computerization out of the reach of most medical offices.

The service bureau sprang up to handle billing for these practices. This was a batch service to which the medical office sent receipts for processing. The service bureau returned the original documents, prepared statements, and delivered reports to the office monthly. By the end of the month, the data was old and inaccurate, since neither new charges nor payments had been entered. If a patient called for a current status, a tedious search through daily and individual records for the updates was required. Hundreds of companies provided these services, with 50,000 practices as clients.

Then a tiny firm, Apple Computers, delivered its first new product — a small, limited microcomputer. And the revolution began as the general applicability of microcomputers moved into small practices. Daring pioneers often made disastrous mistakes as they tried to computerize their offices. But hardware packages providing current information on-line and immediately were attractive. The first systems were financial services replacing the batch systems. Then came insurance processing, general ledger, and payroll.

By today's standards, the systems were simple and crude, providing only the most basic processing. Sophisticated and specialized systems began emerging for different kinds of practices as it became clear that simple systems could not satisfy the diverse needs of complex practices. Hundreds of physicians, seeing the need for good systems for their own offices, joined with analysts to design systems around their needs. As interest in systems grew, these pioneer physicians were encouraged to enter the computer marketplace to sell their systems to all takers. Frequently, the support structure to create, market, deliver, and service software and hardware was meager, and many of these endeavors failed. Added to these packages were those modified for physician office use out of other packages, new systems designed by systems houses or mom-and-pop shops.

Too Many Choices

If the problem used to be a lack of adequate computer systems to handle needs in different types of practices, it is now that there are too many systems and too few standards. Now 3,000 systems, many of poor quality, design, and support, compete for the physician's attention.

It is no wonder that the practitioner who is looking for a system becomes confused. Each system claims to be the solution at a cost of \$395 to 300,000. The solution to what? is the question to ask. The system must satisfy the needs of a particular practice, not the practice next door or another kind of specialty. A system which cannot satisfy the specific needs of a practice is no solution at all and can actually be a hindrance.

Identifying Your Needs

Computerization of the practice has become an attractive solution to handling office paper problems (billing and insurance processing), marketing (word processing and recall), business control (management, activity, compensation, and other packages), access (searching medical data bases and hospital records), and communications (with other offices and other physicians). Together, these form a set of unique features targeted to solving the problems for each office. There is no single solution, no single package that will fit in all offices. The system for general practice is inappropriate in the surgeon's office or in the specialty practice. The single-terminal system which can be useful for the solo practitioner is unsuitable in a multispecialty, multi-location practice. So the problems focus on the selection of the system suitable for each practice.

Selecting a System

Buying a computer may have become an urgent need in your office. The justification in savings, accuracy, and improved medical services can be made easily. Yet a poor decision can be disruptive and destructive to the practice. Inadequate inputting, badly designed reports, file structures inappropriate for office needs, incomplete information, and unusual accounting procedures are problems which can frustrate staff and interfere with operations.

What is important is a selection process which can reduce risks and make the automation transition smooth. Helping you analyze your needs and find that useful system will be the service provided in this column.

Typically, when physicians are looking for a computer, they select certain target services they want the system to handle. Generally, the first capabilities sought are in

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**Dr. Tolos is Executive Director, TEC/Helix and the Health Systems Information Exchange, San Francisco, California.

financial areas; billing, statement generation, insurance claim processing, and provision of financial reports. Sometimes an office is concerned with marketing, so word processing, scheduling, and recall capabilities are required. Physicians interested in diagnosis and treatment features have other needs.

We at TEC/Helix use the patented Pointer System to isolate needs and priorities and to compare systems. In using the system, we will follow the typical automation process in the office. The results will be a precise way of looking at your office and the solutions offered to you.

We will look at the methods and time frames of record keeping and at the utility of good word processing and recall for practice building. Computerized scheduling can make the office more productive or may bog operations down in some instances — we will explain why and when to consider it for your office. Some practices need compensation plans and business systems such as payroll and inventory. In other offices, these are unnecessary. We will tell you why they may not be useful in your office. Some systems allow medical histories, diagnoses, or other clinical information to be entered into patient files. We will help you decide if this capability is worthwhile and describe possible drawbacks.

We will also describe available research applications and their costs to physicians in quest of current information. We will address questions about physical structure of systems, whether single- or multiple-terminal systems are to be used, how offices may be connected, how determinations of what is realistic are made, and how a system is justified. We will devote columns to simple billing and elaborate data bases. We will give guidance and suggestions on interpreting the utility of productivity analysis and on how a system can be tied directly into insurance company systems for on-line claims processing or into hospital systems where the physician has clinical appointments.

Our goal is to help the physician and office manager develop the best method of system evaluation and analysis because we know that the best system will help a practice provide the best medical service.

We want to know your views and problems and will respond to letters through this column. Let us know how we can help you.

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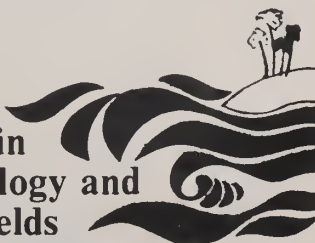
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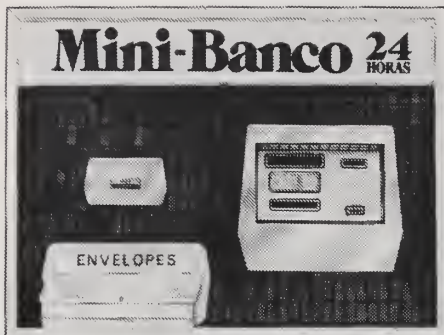
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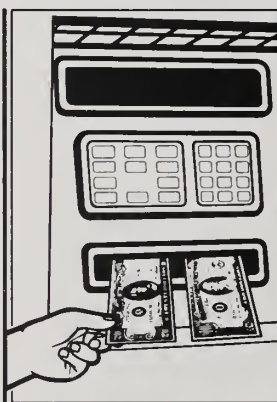
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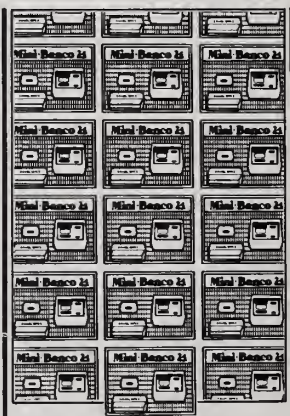
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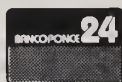
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Motrin Tablets can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

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Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under "Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "Causal Relationship Unknown" if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., FACC*
Amalia Martínez-Picó, M.D., FACC*
Ana Vázquez, M.D.**

Una niña de 6 años de edad con historial de cardiopatías congénitas y cirugía cardíaca paliativa por fallo cardíaco severo, y refractario al tratamiento a los dos meses de edad, se hospitaliza para estudios diagnósticos invasivos.

Está asintomática, sin cianosis, bien desarrollada, bien nutrida y con unos signos vitales normales. Al examen físico se aprecia un PMI en el 4º espacio intercostal izquierdo en la línea clavicular media y se palpa el ventrículo derecho. No hay estremecimientos. Se ausculta un soplo sistólico eyectivo, rudo, grado 3/VI en forma de diamante que termina antes del S₂ y que se aprecia mejor en el 2º-3er. espacio intercostal izquierdo cerca del borde esternal. Este soplo se irradia ampliamente por el precordio. El S₂ se desdobra normalmente y el P₂ está acentuado. No hay visceromegalia y los pulsos periféricos son normales. La Hb es normal, el ECG demuestra hipertrofia ventricular combinada y atrio derecho grande. En la radiografía de tórax no hay cardiomegalia, la vascularidad pulmonar es normal y se aprecia una convexidad en el área de la arteria pulmonar.

Los hallazgos angiocardiógráficos relevantes se demuestran en las siguientes figuras:



Figura 1. Ventriculograma derecho con el paciente en posición lateral.



Figura 2. Ventriculograma izquierdo por vía retrograda con el paciente en posición oblicua anterior izquierda a 60º.

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**Hospital Pediátrico Universitario, Departamento de Pediatría, Universidad de Puerto Rico, Recinto de Ciencias Médicas.

¿CUAL ES SU DIAGNOSTICO?

- Constricción quirúrgica de la arteria pulmonar
- Aneurisma del septo interventricular

Discusión

El diagnóstico inicial de este paciente era: ducto arterioso patente; hipertensión pulmonar, (hiperquinética) comunicación interventricular (CIV) e insuficiencia cardíaca congestiva refractaria al tratamiento médico.

A la edad de dos meses se le ligó el ducto arterioso patente y se practicó una constricción quirúrgica de la arteria pulmonar principal ("pulmonary artery banding"). De esta manera se consiguió disminuir el flujo pulmonar aumentado, reducir la sobrecarga de volumen y controlar la insuficiencia cardíaca que amenazaba la sobrevivencia de este infante. Con la cirugía paliativa se logró proteger al paciente de desarrollar enfermedad vascular pulmonar obstructiva, que es un proceso progresivo e irreversible y constituye la complicación mas temida en la historia natural de la CIV.¹

En los pacientes con CIV grande la presión pulmonar permanece elevada. En ellos no ocurre la regresión normal postnatal de la capa muscular de las arterias pulmonares y persiste una resistencia pulmonar alta.² Estos vasos pulmonares pequeños están estrechos y el flujo pulmonar aumentado a través de ellos produce un roce excesivo con la pared del vaso que ocasiona daño a la íntima arterial. Aparecen cambios proliferativos de la íntima, trombosis secundarias, reducción progresiva de la luz arterial y la consiguiente elevación de la resistencia vascular pulmonar.³ Estos cambios en la íntima no suelen estar presente antes de los seis meses de edad, (excepto en el síndrome de Down con CIV del tipo A-V canal y en la transposición de los grandes vasos) pero su frecuencia y severidad aumenta de los 9 a 12 meses de vida. Estos cambios en la resistencia vascular pulmonar pueden alterar significativamente el curso clínico y la operabilidad de los pacientes con CIV por lo que su valoración es de vital importancia en el manejo de estos infantes.

Por muchos años la constricción quirúrgica de la arteria pulmonar fue considerada como el procedimiento de elección en el manejo de la CIV sintomática en la infancia. Con ello se lograba disminuir el flujo pulmonar excesivo y reducir la presión arterial pulmonar, evitando así el riesgo de desarrollar enfermedad vascular pulmonar obstructiva, a la vez que se controlaba la insuficiencia cardíaca y mejoraba el crecimiento y desarrollo del infante. Sin embargo este procedimiento no está libre de riesgos, ya que posee una mortalidad inmediata variable de un 10 a 25%, a la que debe sumarse la mortalidad que conlleva el remover la banda y efectuar el cierre de la CIV mas tarde.^{4, 5, 6} También puede ocurrir que la constricción quirúrgica quede muy "apretada" resultando en un cortocircuito de derecha a izquierda, o muy "floja", resultando ser inefectiva hemodinámicamente. A lo ya mencionado hay que añadir otros problemas a largo plazo como: el desarrollo de hipertrofia infundibular,⁷ la fibrosis alrededor de la arteria pulmonar, (que ocasiona gradientes persistentes aún después de remover la banda),⁸ así como la dificultad técnica y mortalidad al reconstruir la arteria pulmonar en un segundo acto operatorio.⁹

Con el perfeccionamiento de las técnicas operatorias como el uso de hipotermia con arresto circulatorio limitado,¹⁰ la utilización de equipo quirúrgico moderno especializado para infantes, el mejor conocimiento de las variables post-operatorias en las unidades de cuidado intensivo, los avances en anestesia y terapia respiratoria, junto al uso de nuevos procedimientos, que permiten hacer un diagnóstico temprano, se ha logrado reducir a cerca de un 5% la mortalidad de la CIV en la infancia.¹¹ Esto hace que en la actualidad se favorezca la reparación completa sobre la constricción de la arteria pulmonar como tratamiento de elección en los infantes con CIV sintomáticos.¹² En la mayoría de los centros donde se hace cirugía cardíaca en infantes la única indicación para la constricción quirúrgica de la arteria pulmonar en CIV es en niños muy enfermos, con otra cardiopatías severas asociadas e insuficiencia cardíaca refractoria, en los primeros meses de vida.⁷

La figura 2 nos ilustra un aneurisma del septo interventricular, que constituye uno de los mecanismos de cierre espontáneo de las CIV. Se sabe que la mayoría de las CIV pequeñas cierran espontáneamente y casi siempre lo hacen en los primeros 5 años de vida. Algunos defectos interventriculares grandes pueden también evolucionar al cierre espontáneo,¹³ incluso aquellos que ocasionan fallo cardíaco en la infancia requiriendo constricción quirúrgica urgente de la arteria pulmonar, como el caso en discusión.^{14, 15}

Los mecanismos de cierre de la CIV son varios, a saber: por crecimiento muscular adyacente al defecto; por proliferación del tejido fibroso en los bordes del defecto; por aposición de la valva septal tricuspídea al defecto y por la formación de aneurismas, tanto en la porción membranosa como en la muscular del septo interventricular. Estos aneurismas septales suelen ser pequeños y en su mayoría no ocasionan trastornos hemodinámicos, aunque hemos visto un paciente morir súbitamente donde un defecto de la porción perimembranosa septal cerró por formación de un aneurisma que se invirtió y ocasionó una obstrucción de la arteria coronaria izquierda y el tracto de salida ventricular izquierdo.¹⁶ Recientemente se ha descrito un caso parecido donde la obstrucción fue al tracto de salida del ventrículo derecho.¹⁷ Esta complicación sin embargo es sumamente rara, al igual que la formación de trombos y fenómenos tromboembólicos, en la historia natural del aneurisma septal. También se ha informado recientemente en la literatura médica el desarrollo de estenosis subaórtica discreta en algunos pacientes con aneurisma de la porción membranosa del septo interventricular.¹⁸ El carácter progresivo de esta estenosis sub-aórtica luego del cierre espontáneo de la CIV justifica evaluaciones periódicas si el paciente continúa con un soplo significativo o con trazados electrocardiográficos anormales. Ya que el ecocardiograma bidimensional puede en estos casos demostrar la membrana o la hipertrofia subaórtica, se recomienda este procedimiento para establecer el diagnóstico e instaurar el manejo adecuado en todo paciente en que esta complicación se sospeche.

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Soma[®] (carisoprodol)

Before prescribing 'Soma', consult package circular or latest PDR information, a brief summary of which follows:

INDICATIONS: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS: Porphyrin; allergy or idiosyncrasy to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

WARNINGS: *Idiosyncratic Reactions:* have appeared very rarely within minutes or hours after the first dose of carisoprodol. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation. Symptoms usually subside in several hours, but supportive and symptomatic therapy, including hospitalization, may be necessary.

Pregnancy and Lactation: Safe use has not been established; weigh potential benefits against potential hazards during pregnancy and lactation or in women of childbearing potential. *Usage in Children:* 'Soma' — Not recommended under age 12.

Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g., driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive.

Drug Dependence: Use caution in addiction-prone patients.

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of carisoprodol.

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances.

Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock.

DOSAGE AND ADMINISTRATION: *Adults* — One 350 mg tablet 3 times daily and at bedtime.

OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used successfully with related drug, meprobamate.

HOW SUPPLIED: White, 350 mg tablets in bottles of 100 (NDC 0037-2001-01) and 500 (NDC 0037-2001-03).

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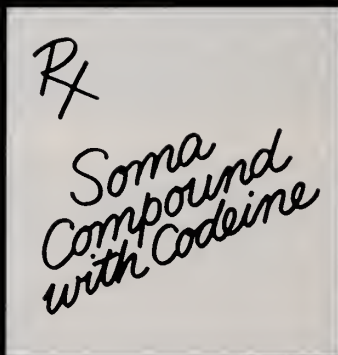
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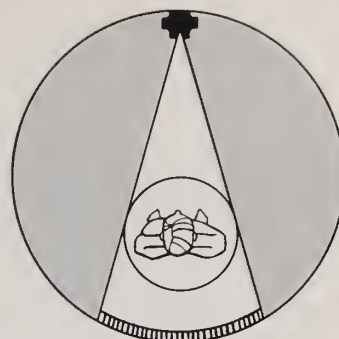
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Warning: May be habit-forming)



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CT Diagnosis



Heriberto Pagán-Saez, MD.*

This is a 62 years old male patient found unconscious in the street. A head CT was done and shown in figure 1.

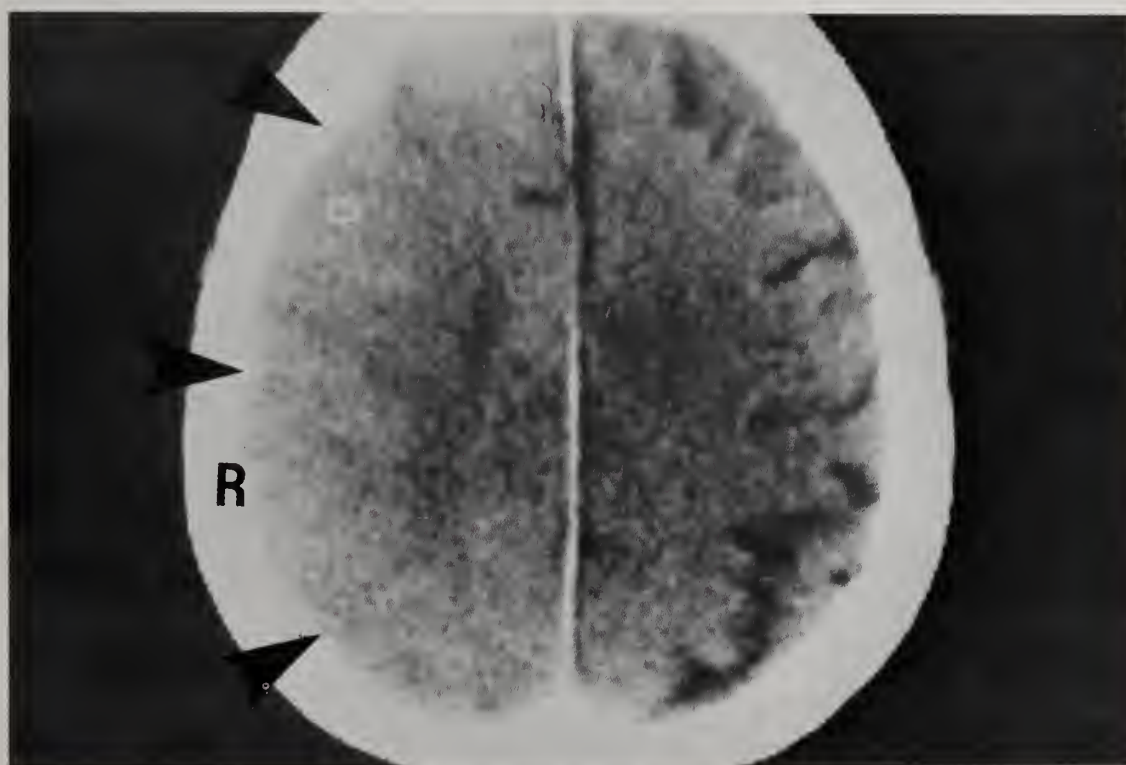


Fig. 1. Scan through the supraventricular plane shows obliteration of the right hemispheric sulci. (see arrows)

What is your diagnosis?

*Director, Department of Radiological Sciences University of Puerto Rico, Medical Sciences Campus, Río Piedras, Puerto Rico.

DIAGNOSIS: Acute subdural hematoma in an atrophic brain.

NOTE: Acute subdural hematoma in an anemic chronic alcoholic patient may mimic a subacute hematoma.



Fig. 2. Scan shows a high density homogenous opacification along the right temporal lobe. (Large arrows) Moderate dilatation of the basal and perimesencephalic cisterns. (Small arrows)

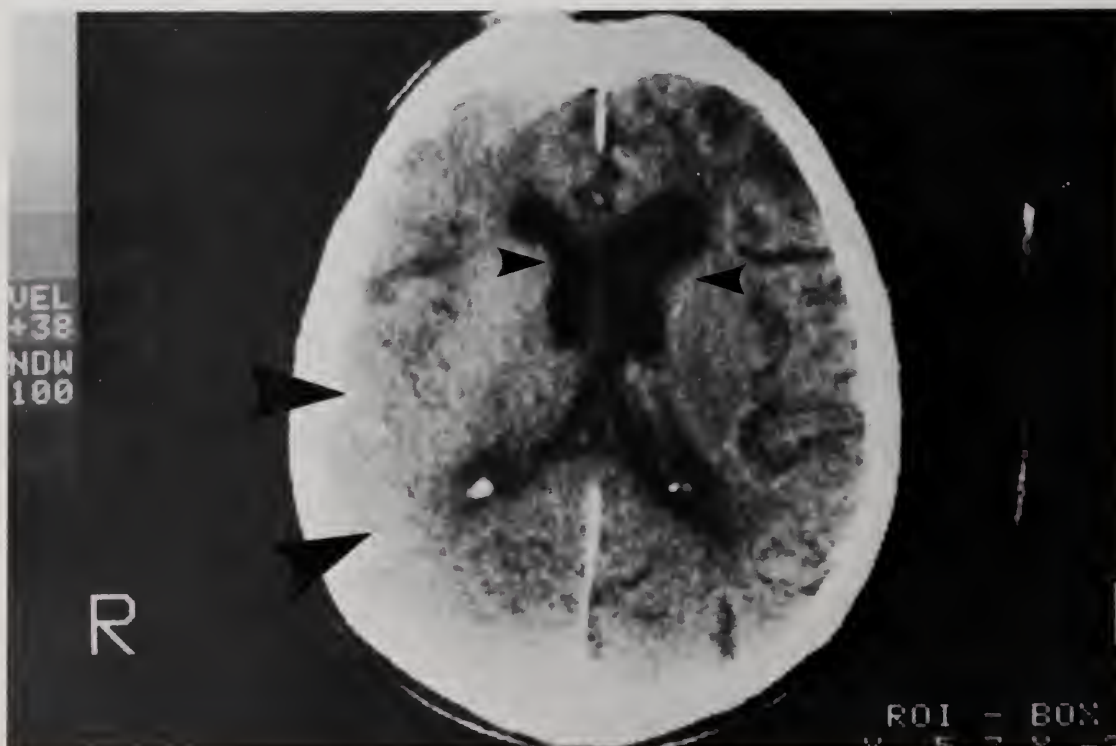


Fig. 3. Scan through the lateral ventricles shows obliteration of right hemispheric sulci. (Large arrows) Moderate hydrocephalia. (Small arrows)

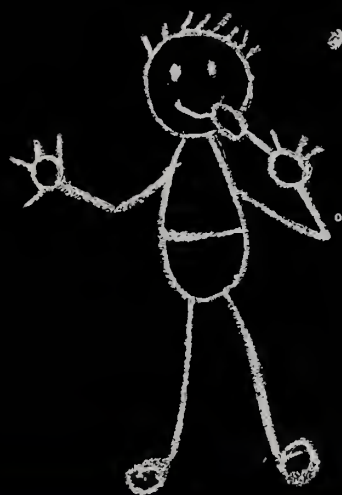
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Also available: scored, titratable

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Each capsule-shaped tablet contains: phenylephrine tannate, 25 mg; chlorpheniramine tannate, 8 mg; pyrilamine tannate, 25 mg.

Please see following page for brief summary of prescribing information.

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that's easy to take

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B.I.D.

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TABLETS
B.I.D.

*Before prescribing, please refer to full product information,
a brief summary of which follows*

Indications and Usage: 'Rynatan' is indicated for symptomatic relief of the coryza and nasal congestion associated with the common cold, sinusitis, allergic rhinitis and other upper respiratory tract conditions. Appropriate therapy should be provided for the primary disease.

Contraindications: 'Rynatan' is contraindicated for newborns, nursing mothers and patients sensitive to any of the ingredients or related compounds.

Warnings: Use with caution in patients with hypertension, cardiovascular disease, hyperthyroidism, diabetes, narrow angle glaucoma or prostatic hypertrophy. Use with caution or avoid use in patients taking monoamine oxidase (MAO) inhibitors. This product contains antihistamines which may cause drowsiness and may have additive central nervous system (CNS) effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Precautions: *General:* Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Antihistamines may cause excitation, particularly in children, but their combination with sympathomimetics may cause either mild stimulation or mild sedation.

Information for Patients: Caution patients against drinking alcoholic beverages or engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery, while using this product.

Drug Interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed with 'Rynatan'.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with Rynatan. It is also not known whether 'Rynatan' can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 'Rynatan' should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 'Rynatan' should not be administered to a nursing woman.

Adverse Reactions: Adverse effects associated with 'Rynatan' at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Note: The following sections are optional and may be omitted.

Overdosage: *Signs & Symptoms*—may vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment—Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used if hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration: Administer the recommended dose every 12 hours.

'Rynatan' Tablets: Adults—1 or 2 tablets.

'Rynatan' Pediatric Suspension: Children over six years of age—5 to 10 ml (1 to 2 teaspoonfuls); Children two to six years of age—2.5 to 5 ml (½ to 1 teaspoonful); Children under two years of age—Titrate dose individually.

How Supplied

'Rynatan' Tablets, buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and bottles of 500 (NDC 0037-0713-96).

'Rynatan' Pediatric Suspension: dark-pink with strawberry-currant flavor, in pint bottles (NDC-0037-0715-68).

Storage: 'Rynatan' Tablets—Store at room temperature, avoid excessive heat—(above 40°C/104°F).

'Rynatan' Pediatric Suspension—Store at controlled room temperature—between 15°C–30°C (59°F–86°F); protect from freezing.

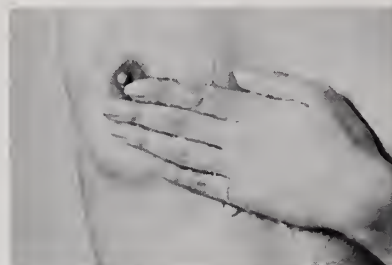
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Read this like your life depends on it.

Breast cancer found early and treated promptly has an excellent chance for cure. About a week after your period, practice this self-examination.



1. In bath or shower.

Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

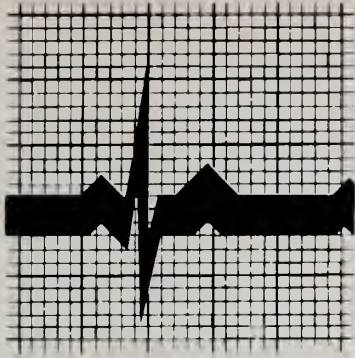
Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.





ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, M.D., FACC

This 20-year-old female, slightly mentally retarded, has been followed at the Puerto Rico Medical Center since the age of 2 years. Symptoms and signs over the years have comprised easy fatigability, chest pain, dizziness, premature puberty, hypertelorism, low set ears, a broad forehead with a funny face, bacterial endocarditis, chest deformity, a pulse of 44 per minute, regular "cannon waves" in the neck, and systolic and diastolic murmurs in the third-fourth left intercostal spaces at the mid-clavicular line. Chest roentgenograms in recent years have shown cardiomegaly and prominent pulmonary arteries with increased pulmonary vascular markings. Studies have revealed a bifid left kidney and polysplenia.

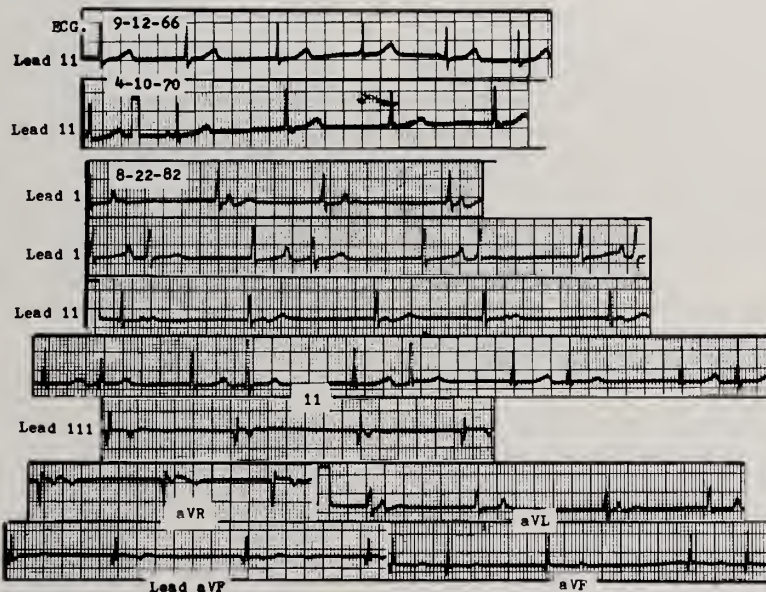


Figure 1A

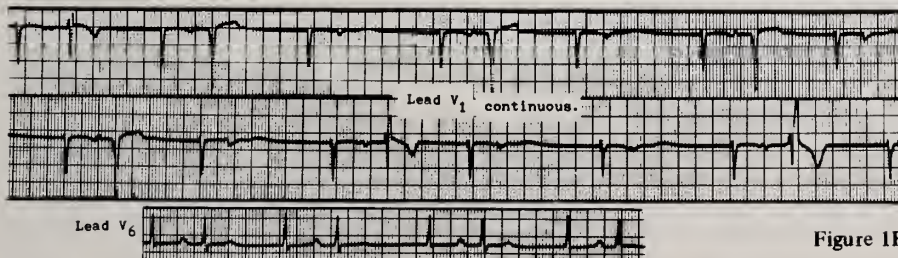


Figure 1B

Questions

1. What are the electrocardiographic diagnoses?
2. What are the cardiovascular diagnoses and syndrome?
3. What is the pathogenesis of the electrocardiographic findings?

Invasive and non-invasive procedures showed the following diagnoses:

- **Interruption of inferior vena cava (IVC)** with azygous vein draining into a left superior vena cava (SVC). Left SVC drains into the coronary sinus.
- **Malrotation of abdominal viscera**- small bowel on the right side, colon on the left side, the right colonic flexure was high in the abdomen. Liver scan: distorted image, left lobe prominent, anterior and extends to the left upper quadrant.
- **Partial intestinal obstruction**- Excision of duodenal web causing obstruction, at age 6 years.

Electrocardiograms (ECG)

Sinus node dysfunction.

9-12-66, Lead II. Sinus arrhythmia with isorhythmic atrioventricular (AV) dissociation and junctional escape rhythm.

4-10-70, Lead II. Same, followed by AV junctional escape rhythm with retrograde atrial conduction in the last three beats.

8-22-82, Complete ECG. Sinus arrhythmia and bradycardia, junctional arrhythmia. P rate 31-48, QRS rate 32.6-54 per minute. Incomplete AV dissociation with phasic aberrant ventricular conduction (Incomplete right-incomplete left-incomplete right- complete right bundle branch block in lead V₁). Possible 2:1 sinoatrial block. A type of escape-capture bigeminy.

The expected inverse R-P:P-R interval relationship prevails. The R-P is shorter and the P-R interval longer for the right bundle branch block beats, while the converse applies for the left bundle branch block beats. Sinus beats with a shorter R-P interval are not conducted.

The R-R interval following a sinus capture beat is foreshortened. This is stated (Pick and Langendorf) to be common in incomplete AV dissociation, indicating that distal to the site of the junctional pacemaker, capturing and automatic impulses share a common path, in which conduction velocity of the "prematurely" occurring capture beat is delayed. Thus, the shortening of the manifest first automatic cycle is only apparent.

Differential Diagnosis - Except for the trace of 4-10-70, the rhythm reflects incomplete AV dissociation with sinus capture beats of the ventricles, and not junctional reciprocal (echo) beats, nor subatrial reentry of retrograde impulses in junctional rhythm, although the premature beats do occur after junctional escapes with prolonged R-P intervals. The P axis is leftward, -10° (see aVF), but not in the reciprocal P¹ range of -90° to -110° . On other traces the sinus P wave falls in front and inside the QRS complex.

Discussion

Certain electrocardiographic abnormalities are associated with particular congenital heart disease (CHD).

Congenital anomalies are: the Polysplenia syndrome, which may have bilateral leftsidedness, infra- or hepatic interruption and absence of the IVC with azygous vein continuation (prominent azygous), persistent left SVC (bilateral SVC's -suggest atrial isomerism), sinus venosus atrial septal defect, cardiac malposition, abdominal heterotaxia, partial malrotation of the bowel, indeterminate visceral situs, horizontal midline symmetrical liver, anomalous pulmonary venous connection, isomerism of organs, AV canal defects, common atrium, ostium primum defect, truncus arteriosus, pulmonary atresia and stenosis, single ventricle, ventricular septal defect, double outlet right ventricle and hypoplasia of the left-sided chambers. Approximately 25% of cases of polysplenia have no significant cardiac anomaly except for absent IVC and abdominal heterotaxia. A persistent left SVC has a prevalence of 0.3-4.3%. An absent IVC with azygous continuation is very rare in a normal heart, but occurs in 0.6-2.9% of cases of CHD, and in 20% of patients with CHD and situs inversus. Genito-urinary anomalies occur in 15% of cases.

Classic ECG abnormalities in this syndrome are: sinoatrial node arrhythmias and cardiac electrical instability; a superior and leftward P wave vector (-30° to -90° , negative P waves in leads II, III, aVF ("coronary sinus rhythm") is common-left atrial isomerism. Thirty-80% of patients with persistent left SVC and 67% of those with an absent IVC have a superior P vector; left atrial rhythm, wandering pacemaker; supraventricular tachyarrhythmias; intermittent AV dissociation; complete sinus arrest or sinoatrial block with a slow and uneven left atrial pacemaker competing with repetitive nodal escapes for command of the heart. A superior QRS axis is present in one-third of the cases.

Pathogenesis: an abnormal sinoatrial node, which may be absent, aberrant or ectopically located, or bilateral sinoatrial nodal tissue; escape mechanism with change to accessory sinus nodal tissue. In two cases of left SVC and cardiac electrical instability, James and Edwards found histological abnormalities in the sinoatrial node and its artery, the AV node and the bundle of His.

Recognition of these ECG patterns and syndrome are important in that they serve as clues for certain CHD, they may complicate cardiac catheterization and cardiac surgery, and they may favor mis-diagnosis of atrial inversion.

A similar ECG pattern as observed in this patient, was present in Case 2 of Hastreiter and Rodríguez-Coronel.

Villavicencio and associates (see references 12, 14) have made a significant contribution in reporting their experience in Puerto Rico with the Asplenia-Polysplenia Syndrome. The wide variety of expression in its clinical, electrocardiographic and radiographic manifestations have been reported by him in the patients of the Pediatric Cardiology Section at the former University Hospital.

Acknowledgement

The author wants to thank the Pediatric Cardiology Section of the University Children's Hospital for the data provided in the preparation of this paper.

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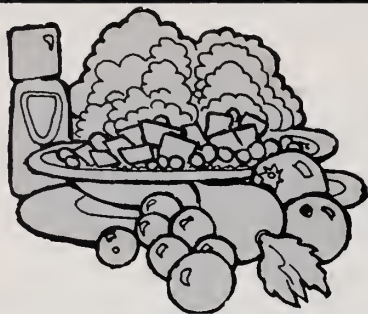
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MEDICAL ASPECTS OF NUTRITION

The Fetal Alcohol Syndrome*

Eileen M. Ouellette, M.D.**

Fetal Alcohol Syndrome (FAS) refers to a series of effects seen in children of women who chronically drink alcohol to excess during pregnancy.^{1, 2, 3} Minimum criteria for the diagnosis of FAS are:⁴

- 1) Prenatal and/or postnatal growth retardation with weight, length and/or head circumference below the tenth percentile;
- 2) Central nervous system involvement with neurologic abnormality, developmental delay or intellectual impairment; and,
- 3) Facial dysmorphism (birth defects) with at least two of the following three signs:
 - Microcephaly
 - Microphthalmia and/or short palpebral fissures
 - Poorly developed philtrum (the distance from the base of the nose to the upper lip), thin upper lip, and/or flattening of the maxillary area.

Fetal Alcohol Effects (FAE) refers to any abnormalities seen in children as a result of heavy or moderate alcohol use by women during pregnancy, when the full syndrome is not present in their offspring. *As little as two drinks a day has been associated with an increase in premature infants.*^{5, 6}

In addition to the congenital malformations reported in FAS, a number of behavioral effects have been noted in FAS and FAE. Children often have an *attention-deficit disorder, with or without hyperactivity. They have trouble focusing and are easily distractable.* Some of these children respond to stimulant medications. Scientific research shows it is generally impossible to predict in advance which children will be responders, so a trial of medication should be done in appropriate cases.

Many children with FAS and FAE have learning disabilities (LD). These often do not adhere to the more classical LD patterns, but children show a scattering of abilities without any definitive areas of strength or weakness. *Many children with FAS and FAE also have problems with gross and fine motor coordination.* Many children with these problems are first identified as having FAS and FAE by their kindergarten teachers. The more mild the symptoms of FAS and FAE, the more likely is the diagnosis to be delayed.

Although there has been anecdotal information concerning the ill effects of maternal alcoholism dating to antiquity, and although the English Parliament in the eighteenth century conducted studies which substantiated this belief, this knowledge was lost. FAS was first described in modern times by Jones, et al., in 1973 in eight unrelated children of chronic alcoholic mothers.^{1, 2} Its existence has since been verified in numerous studies.^{3, 4, 5, 6, 7, 8, 9, 10}

Frequency of FAS

FAS is estimated to occur between one and two per thousand live births for the full constellation of features. Frequency of partial expression may be between three to five per-thousand live births. It is believed to be the most common cause of mental retardation.^{7, 8} *FAS is totally preventable.*

Effects produced range from mildly impaired to profoundly afflicted children and some fatalities have been reported. The degree of risk of producing an abnormal child for a mother with alcohol abuse is unknown. It has been well shown in animal studies that the fetal effects of alcohol are dose-related. That is, the more alcohol is consumed by the pregnant animal, the greater the effects on the offspring. Once a certain percentage of the diet is replaced by alcohol, there is no survival of the offspring and stillbirths and fetal resorption occur. This lethal percentage appears to differ for different species. Good human survival data are not currently available, nor is there any information on whether there is decreased survival of FAS children to age 1 year.

In human studies, the same effect has been demonstrated, but quantitative data are not currently available.

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**Director, University Affiliated Facility, Eunice Kennedy Shriver Center, Waltham, Massachusetts 02154, Assistant Professor of Neurology, Harvard Medical School, Assistant Neurologist Massachusetts General Hospital, Boston, Massachusetts 02114

Human studies also suggest that the longer a woman drinks, the greater is the risk to the offspring. If a woman continues to drink heavily, there appears to be a greater risk to the fetus with each successive pregnancy.

Studies on moderate drinking during pregnancy, equivalent to a daily consumption of 2 ounces of 100-proof whiskey, show an association with lower birth weight in offspring and increased prematurity rates.^{9, 10, 11} Binge drinking has also been reported to cause harmful effects in animal research, but well-controlled studies of its effects are not yet available in humans. Safe levels of alcohol intake during pregnancy, if any, have yet to be determined.

At the present time, it is recommended that pregnant women abstain from alcohol, but an occasional alcoholic beverage has not been found to be harmful to the fetus. Similar recommendations are made to nursing mothers.

Maternal/Child Effects of Alcohol

Alcohol passes rapidly from the maternal circulation to the fetus and assumes approximately the same concentration as in maternal blood.^{12, 13} Alcohol levels within the fetal circulation fall more slowly than in the maternal circulation, so that detectable levels of alcohol are still present in the fetus after the alcohol has been totally cleared from the maternal circulation.¹⁴

Not only does alcohol enter the fetal circulation but it is excreted into the amniotic fluid where it remains in essentially the same concentration for several hours until slowly being cleared. Changes are seen in fetal acid-base balance, cerebral function and metabolism.

Alcohol also has been found to reach human milk in a similar concentration to that in peripheral maternal blood, decreasing together with decreasing ethanol content of the blood.¹⁵

Treatment of FAS

It must stressed again that FAS and FAE are a totally preventable cause of growth abnormalities, congenital malformations and mental retardation. Intensive prevention strategies should be undertaken as there is no known way to reverse or reduce the effects of alcohol on the fetus once they have occurred. Once a baby has been born with signs of FAS, early identification of the problem, treatment for specific clinical findings, infant stimulation and close attention to nutritional problems are vital.

Research shows much of the postnatal growth retardation seen in these children is due to their poor food intake. As newborns, children have increased, but uncoordinated, sucking and swallowing movements coupled with extrusion movements of the tongue, so that their intake of food is less than adequate and feeding times are prolonged. Even highly experienced foster mothers find FAS children extremely difficult to feed.

Generally, feeding problems are significant for the first year of life and gradually improve so that by the time the children are 3 to 4 years of age they are consuming a more adequate diet, although they often continue to be highly selective in their food preferences.

Newborn infants with FAS or FAE should be evaluated by a nutritionist prior to discharge from the

nursery and mothers should be instructed in feeding techniques. Arrangements should be made for inhome follow-up at least weekly by a visiting nurse or other health professional to monitor feedings and other problems. Frequent contact with a nutritionist should be maintained. Babies should be seen more frequently by their pediatricians and weight gain carefully measured to monitor for failure to thrive.

If poor feeding becomes a significant problem, it is sometimes useful to have mothers and children seen in a feeding clinic, where an interdisciplinary team of professionals can evaluate the problem. Videotapes of the mother feeding the baby are extremely useful in determining the nature of the problem. In many cases, uncoordinated swallowing movements persist and food is extruded by the tongue, rather than swallowed.

Babies may be fussy as a result of poor food intake and prolonged feeding times. It is important that counseling is available to the mothers, as they sometimes feel inadequate as mothers because of the baby's feeding difficulties and may return to alcohol abuse to assuage their guilt.

Prevention of FAS

The ideal time to prevent FAS and FAE is prior to pregnancy. Young women of childbearing age should be taught in high school health classes about the risks of drinking alcohol during pregnancy. Colleges should make information about FAS and FAE available to their students. Women who are planning pregnancies or are sexually active and do not use effective contraception should decrease their alcohol intake to minimal amounts or abstain totally. The first few weeks of pregnancy are those during which major organ systems form. High alcohol intake during these weeks may have serious effects on the baby even before the woman is certain she is pregnant.

Four sites are especially useful in the identification of women of child-bearing age who have alcohol-related problems. Obstetricians' offices, family practitioners, family planning and prenatal clinics are ideal locations for educational programs and places where women with alcohol problems should be identified.¹⁶

Questions about alcohol use should be routinely asked of women at the first prenatal visit. Although many individuals with alcohol problems will underestimate the amount of their drinking, a brief questionnaire developed by Rosett, et al., has been found useful in identifying moderate and heavy drinkers in a nonthreatening manner.¹⁷

10 - Question Drinking History for Prenatal use

Beer:	How many times per week?	_____
	How many cans each time?	_____
	Ever drink more?	_____
Wine:	How many times per week?	_____
	How many glasses each time?	_____
	Ever drink more?	_____

Liquor: How many times per week? _____
 How many drinks each time? _____
 Ever drink more? _____

Has your drinking changed in the last year?

Pregnancy is an ideal time for initiating intervention in women previously unidentified as having alcohol-related problems.¹⁸ Women so identified should be referred to alcohol treatment centers for additional counseling and support. Pregnant women are generally highly motivated to alter their drinking behavior in order to produce offspring with the least possible risk. Women who drink heavily but stop drinking during pregnancy have a good chance of delivering a normal child. Although no improvement in the risk of congenital malformations could be expected due to their appearance early in the pregnancy, the risk of prematurity and growth retardation is lessened.³

Summary: Within the last 10 years, scientists have re-discovered the devastating effects of alcohol on fetal development. Much remains to be learned about the cause and scope of the problem. Unlike genetic disorders, FAS is totally preventable.

Our best weapons in combatting this important public health problem are:

- 1) Early identification and treatment of women of childbearing age with alcohol problems;
- 2) Prompt diagnosis and therapy of children with FAS; and,
- 3) Early and increased public awareness.

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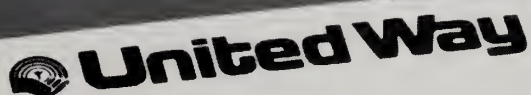
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Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN.

Precautions: ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyl dopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients.

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Dietary Management of Diabetes Mellitus*

Alan Chait, M.D.**

Although dietary measures have long been accepted as an essential component in the management of the patient with diabetes mellitus, it is only recently that has been general agreement as to the principles and practices that determine the diabetic diet. While many of these principles and their scientific basis have long been known, their general acceptance and widespread application have been slow in evolving. Perhaps the two most important changes in attitude over the years are the realization that increased flexibility is likely to be associated with improved compliance and that the liberalization of the intake of carbohydrate is likely to do more good than harm. Despite agreement on many aspects of the diabetic diet, some issues remain contentious. Dietary recommendations are likely to further evolve with increasing knowledge of the pathogenesis and natural history of diabetes.

Goals of Therapy

The ideal diet for the patient with diabetes should (1) help normalize the metabolic abnormalities associated with the diabetic state, and (2) should be of value in the prevention of the macrovascular and microvascular complications to which diabetics are so prone. While an attempt is made to achieve these goals, the diet should nonetheless be acceptable to the individual taste of the patient. The diet should take into account any special considerations that may be operative in that specific case and should cause minimal disruption to the patient's lifestyle. Clearly, this requires individualization within a framework based on patho-physiological considerations.

Calorie Content and Timing of Meals

Calorie content of the diet needs to be tailored to the needs of the individual and may change as conditions change. Perhaps the single most important consideration is the patient's body weight. Thus, the overweight noninsulin-dependent diabetic (NIDDM) should restrict calorie intake in an attempt to achieve ideal body weight. By so doing, insulin resistance, which is the hallmark of this type of diabetes and which appears to play an important causal role, is reduced. Reduction in insulin resistance, which results from calorie restriction, may be all that is required for normalization of the metabolic abnormalities seen in many cases of obese NIDDM.

By contrast, the thin patient with insulin-dependent diabetes (IDD) will not benefit from calorie restriction and should be provided with ample calories. This is of particular importance during periods of increased requirements, such as during growth and development and during pregnancy and lactation. Indeed, much of the impaired growth associated with IDD in the past may have been the result of undernutrition due to caloric restriction. Thus, the normal-weight diabetic should receive a nutritionally sound diet that provides enough calories for the needs of the body, but which does not result in weight gain.

Timing of meals is perhaps the single most important practical consideration in the patient with IDD, but it also is important in the patient with NIDDM who is receiving insulin. In individuals receiving insulin, the delivery of insulin to the body is dictated by the type of insulin being used (i.e., whether long, intermediate or short acting), the timing of the insulin injections and the method of insulin delivery (i.e., by conventional therapy or by pump). Thus, carbohydrate needs to be delivered in response to the level of circulating insulin in the body, rather than the opposite, as occurs physiologically. When insufficient glucose relative to insulin is present in the circulation, hypoglycemia ensues. Because of the brain's dependence on an adequate blood glucose level for normal function, avoidance of hypoglycemia should be a primary goal in all diabetic patients. Recurrent episodes of hypoglycemia can result in brain damage.

Therefore, with diabetics taking insulin, frequent intake of carbohydrate will tend to result in small excursion of the blood glucose level and will help to prevent hypoglycemia. As a general rule, diabetics receiving conventional insulin therapy should consume some carbohydrate approximately every three hours during their waking hours to achieve this end. Clearly, this should not be at the expense of their calorie intake, rather the total amount of calories appropriate for the patient should be spread more evenly throughout the day. This translates into more frequent, but smaller, meals or snacks. Further, a bedtime snack, which is of value in the prevention of the all too prevalent nocturnal hypoglycemia, is an important component of the meal plan.

Patients who are receiving their insulin by pump, or those on multiple injections of regular insulin, have much more flexibility in the timing of their meals. In such cases, the patient can control the timing of the insulin delivery and the dose of insulin to be appropriate for the time and size of the meal.

**Contemporary Nutrition*, Vol. 9 No. 2, February 1984. Reprinted with permission from General Mills Inc., Minneapolis, Minnesota.

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Carbohydrate and Fat Content

Because of the hyperglycemia that characterizes the diabetic state, carbohydrate-restricted diabetic diets have been in vogue for many years. However, the scientific basis for this approach is unsound. The beneficial effect of carbohydrates on insulin sensitivity had been demonstrated as early as the 1930s and has been rediscovered periodically with increasing sophistication since then. However, it has only been within the last few years that there has been widespread acceptance that carbohydrate restriction is unnecessary in the diet of diabetics.

A statement that a diet relatively high in its carbohydrate content is advisable for virtually all diabetics was made in special reports by the American Diabetes Association Committee on Food and Nutrition published in 1971 and again in 1979. Similar statements have been published by comparable diabetes groups in many countries throughout the world. Gradually, this change is being adopted by physicians, dietitians, diabetic counselors and by diabetic patients themselves.

Diets that are proportionately high in carbohydrates have been shown to actually improve blood glucose control by enhancing insulin sensitivity, provided adequate insulin is present. Thus, for the patient with IDD who is well controlled on insulin, and for the individual with NIDD in whom endogenous insulin levels are normal or high, carbohydrate-rich diets have both theoretical and practical application. But perhaps more important than the effect of such diets on blood glucose regulation is their potential effect in reducing the alarming frequency of cardiovascular complications—the leading cause of death among diabetics today. If the total calorie intake of the diet is to remain unchanged, an increase in the proportion consumed as carbohydrate needs to be offset by a reduction in other components. This is best achieved by a reduction in fat calories, particularly in the form of saturated fat. High intake of fat in the diet of diabetics during past years may well be an important factor in the dramatic increase in cardiovascular complications seen in these patients. Thus, to attempt to reduce this predisposition to atherosclerotic complications in the diabetic, a diet that is low in its content of saturated fat and of cholesterol is likely to be of benefit. Such a diet will lower plasma levels of cholesterol and triglycerides, elevations of which are associated with an increased risk of coronary artery disease in the general population as well as in diabetics. It therefore seems especially prudent to use such a diet in the diabetic, in whom atherosclerosis occurs more severely and at an earlier age than in the nondiabetic. However, proof that the use of such high carbohydrate, low fat diets actually reduces the incidence of these complications in the diabetic is not available presently and will only emerge as the result of long-term studies.

Type of Carbohydrate

For years, the dogma has been to limit the intake of simple sugars by diabetics on the assumption that they were all rapidly absorbed and resulted in marked postprandial swings in blood glucose concentrations. Recent

evidence disproves this dogma since certain foods that are rich in complex carbohydrates result in far greater excursions of the blood glucose than do some foods that are rich in simple sugars. A knowledge of which simple and complex carbohydrates lead to the greatest changes in glucose levels is desirable. However, the wholesale restriction of simple sugars in the diet of the diabetic is without scientific basis. Therefore, recommendations need to be changed.

Other Components of the Diet

Intake of protein, vitamins and minerals should be the same as in any wellbalanced diet, although special attention to ensure an adequate intake of calcium is necessary to help prevent osteoporosis to which diabetics appear to be particularly susceptible. In view of the predisposition of the diabetic to heart disease, it also is prudent to limit the intake of salt in an attempt to prevent hypertension of those predisposed to salt-sensitive hypertension. A low salt intake certainly is advisable in diabetics who already are hypertensive.

Alcohol

Moderate use of alcohol is not contraindicated in most diabetics. However, alcoholic beverages tend to be high in calories, which need to be restricted in the overweight patient. Also, some diabetics are exquisitely sensitive to the hypertriglyceridemic effect of alcohol. These patients usually have elevated baseline triglyceride levels that can easily be measured. Alcohol should not be consumed by the diabetic on an empty stomach, since alcohol inhibits gluconeogenesis and serious hypoglycemia can result, particularly in patients taking insulin.

Fiber

Use of high fiber foods has been advocated by some in slowing the absorption of carbohydrates, thereby minimizing blood glucose excursions through the day. However, the advantage of a high carbohydrate diet on blood glucose levels is independent of the fiber content of the diet. Specific advantages of a high fiber diet remain controversial and further evidence of a beneficial effect of fiber is required before the widespread pharmacological use of fiber supplements can be recommended.

Sweeteners and Special Diabetic Foods

There is no general agreement concerning desirability or acceptability of sugar substitutes. Nutritive sweeteners, such as fructose, xylitol and sorbitol, and nonnutritive sweeteners, such as saccharine and the recently released nutritive sweetener aspartame, are widely used by diabetics who wish to sweeten their diets without the use of sucrose or glucose. While some of these sugar substitutes may help reduce calorie intake, their safety and efficacy for diabetics requires further testing.

Since there is no reason why the above dietary principles cannot be applied using regular foods, the need for the more expensive, specialized diabetic foods is questionable.

Other Strategies

Exercise by the diabetic may be beneficial from a number of standpoints. Reducing insulin resistance in the patient with NIDD may play an important role in blood glucose regulation and in weight loss. Exercise may also be beneficial in reducing the risk of cardiovascular disease. However, since exercise tends to lower blood glucose concentration, insulin dosage may have to be adjusted to prevent hypoglycemia.

Summary: Since dietary regimes in diabetics need to be practiced lifelong, every effort should be made to facilitate acceptance of the recommendations made and, hence, compliance. A flexible approach that takes into consideration the patient's life-style, socioeconomic and ethnic factors, food preferences and personality has a much greater chance of success than the dogmatic and rigid approaches that have been practiced in the past.

Finally, time spent on patient education is likely to reap rewards. The well-informed diabetic patient is the most important member of the team necessary for successful long-term management of diabetes.

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ASAMBLEA DE LA ASOCIACION MEDICA DE PUERTO RICO 1910



Esta Asamblea celebrada en Ponce fue un verdadero acontecimiento médico desinados a señalar en los anales del cuerpo médico puertorriqueño, nuevos y beneficiosos rumbos, tanto en el orden científico, como en el de los intereses morales y materiales de la profesión.

Pusiéronse en ella a discusión asuntos de vital importancia, entre ellos el de la incorporación de esta Asociación a la nacional. Este asunto había quedado pendiente en la anterior asamblea, fue rudamente combatido, terciando en el debate distinguidos médicos, entre ellos los señores González Martínez, Gutiérrez Igaravidez y Gutierrez Ortiz, que defendían el tema en contra los Dres. Quevedo Báez, Coll y Toste y Matanzos. El discurso de tonos vibrantes y patrióticos del Dr. Quevedo Báez, fue decisivo, quedando derrotado el proyecto.

Ocupóse también de la Ley de Sanidad para Puerto Rico que fue aprobada por la Cámara en la anterior legislatura y que volverá a estar sobre el tapete, porque la Asociación Médica tiene interés en demostrar

de Sanidad, frente a la imposición y prejuicio que establece el Bill Olmsted, recientemente discutido en la Cámara Nacional.

Hízose también la Reforma del Reglamento, se organizó un arbitrio para certificaciones médicas y se estudió, aunque sin llegar a aprobarse el proyecto de un Montepío médico que quedó aplazado para la próxima asamblea.

Otro de los proyectos de verdadera importancia fue el de la reorganización de los Delegados de Distrito, presentado por el Dr. Zabala, en cuya virtud estos funcionarán con relativa autonomía dentro de la Asociación, con atribuciones para crear subjunatas y celebrar sesiones científicas y de carácter administrativo.

El Dr. Eliseo Font y Guillot, Presidente de la Asociación Médica, merece honores por el tacto y alto sentido con que desenvuelve los destinos de una institución tan prestigiosa en el país. Nuestra enhorabuena.



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AMERICAN ACADEMY OF PEDIATRICS

ON RAISING A "SUPERBABY": SPARE THE FLASHCARDS, NOT THE CHILD

You may have seen these scenes before: an insistent parent bearing flashcards, just waiting to pounce on an unsuspecting offspring crawling on the floor.

Or perhaps a mother taking a training course to teach her infant to swim, read, do math, speak a foreign language or play the violin by the age of two.

Though a mom or dad might have good intentions about raising a "superbaby", is it best for the child? Can a child get burned out on excessive learning at an early age?

According to George Sterne, M.D., head of the American Academy of Pediatrics' Committee on Early Childhood, it is more important for your child's well being to receive a rich and emotionally supportive atmosphere than to get the infant/toddler on the fast track to success through early education.

Other experts agree. Noted Boston pediatrician, T. Berry Brazelton, M.D., has been quoted to say that what a baby needs most of all "is somebody who cares about him as a person, and who will pay attention to his individual needs and will foster them".

Learning, Dr. Sterne continues, is a natural concept and should be pleasant. And unstructured play, though simple in nature, is very important to the child's development

Young Health, AAP, Fall 1984

PERTUSSIS VACCINE

A review of the current data on the frequency and severity of pertussis and also of reactions occurring following administration of pertussis vaccine have led to some changes in recommendations for immunization with pertussis vaccine. Continued efforts to immunize those who should receive vaccine are essential as pertussis

produces significant morbidity and may even be fatal; it is particularly severe in those who are unimmunized. The curtailment of pertussis immunization has resulted in epidemics in some countries.

Increased Risk of Convulsion Following Vaccine

Children who should not receive additional doses of pertussis-vaccine

Children who have a seizure within 48 hours following the receipt of a pertussis-containing vaccine, eg, DTP, should not receive additional doses of pertussis-containing vaccines. The risk of first seizures following pertussis vaccine appears to be approximately 1/1,750 immunizations.

Children who might have immunization deferred

1. Children who have had a personal history of convulsion at any time appear to have an increased risk of convulsions following receipt of pertussis-containing vaccines. The exact frequency of seizures following DTP in children who have had a previous personal history of non-pertussis-vaccine-associated seizure is unknown.

2. Children with certain neurologic conditions (eg, tuberous sclerosis, certain inherited metabolic defects, and other conditions), that might predispose to seizures may be at increased risk of convulsions following receipt of pertussis-containing vaccines.

Conditions of Uncertain Risk of Convulsion Following Immunization

It has been suggested that the risk of convulsions following receipt of pertussis vaccine is increased if there is a family member who has a nonfebrile seizure disorder, or if a sibling has had a seizure following receipt of a pertussis-containing vaccine.

Risk of Exposure to Pertussis

1. Infants who attend day care centers or participate in other activities in which there is increased close contact with other young infants are at greater risk of being infected with a variety of infectious agents that are endemic to their setting or prevalent in the community.

2. Infants and children enrolled in programs or who reside in institutions for the neurologically impaired.

3. There is a significant risk of exposure to pertussis in many underdeveloped countries, in many parts of the western hemisphere including parts of Canada and some developed countries, eg, England, Japan, and others.

4. At the present time, the risk of exposure to pertussis in most areas in the United States is relatively low.

Immunization Schedules

In children who are to have pertussis immunization deferred, pediatric diphtheria, tetanus toxoid (DT), should be given in lieu of DTP. If started after 1 year of age, two rather than three doses are to be given followed by a third dose 1 year later.

Reassessment of Children for Whom Immunization was Deferred

1. Immunization after infancy of those in whom it has deferred is of considerable value.
2. Deferred pertussis immunization should be reevaluated at each office or clinic visit.

Contraindications for Pertussis Immunization

Pertussis immunization is contraindicated for those who have after administration of a pertussis-containing vaccine: (1) a severe neurologic reaction; (2) persistent inconsolable screaming for three hours or more; (3) a hyporesponsive, shock-like state; (4) temperature of 40.5°C (105°F) within 24 hours following immunization; (5) a convulsion within 48 hours following immunization; or (6) an allergic reaction to the vaccine.

Fractional Doses of Pertussis Vaccine

1. Giving smaller than recommended doses to those with "contraindications" cannot be recommended.
2. Giving smaller doses at different visits will reduce local reactions but may also reduce serologic response.

Pediatrics Vol. 74 No. 2 August 1984

INCREASED USE OF PESTICIDES POSES MORE HAZARDS TO CHILDREN

Parents who bring industrial strength pesticides home from work may, in fact, be putting a child's life in danger, says an environmental expert.

Richard Jackson, M.D., a pediatrician and chief of the California Dept. of Health Services' Community Toxicology Unit in Berkeley, says that many low toxicity chemicals of the past have been replaced by far more toxic, but less environmentally damaging pesticides.

"If these chemicals are not safely stored or properly used, a teaspoon ingestion can have tragic consequences, particularly if they go unobserved," Dr. Jackson said. Presently, 1,200 active ingredients in 30,000 products are used in the marketplace each year.

Because many of the present-day pesticides degrade rapidly, they pose little health hazards just days after they've been applied. Of particular concern to him are less acutely toxic substances that are tetratogens, which cause birth defects in animals and are easily absorbed through the skin.

"Though better analytical methods to measure pesticide residues are available, as are improved methods to carry out cancer risk assessments, concerns remain," Dr. Jackson remarks. "Experts and the public should ask, 'How well were these chemicals tested?' The majority of chemicals registered lack complete acute and chronic toxicity data, but continue to be sold because they were 'grandfathered' in," he said.

To help protect children from home pesticide hazards, Dr. Jackson suggests that parents always read the label on what they use, store and use it safely, keep the chemicals away from children and last, but not least, find out if the pesticide is safe to use.

AAP News Release- September 19, 1984

PEDIATRICIANS WANT TO SEE BOXING BECOME A THING OF THE PAST

The future of a young boxer rising from poverty to fame and fortune more often results in slow progressive brain injury than in financial gain. Because the frequency of chronic brain damage is an increasing concern in the medical community, the American Academy of Pediatrics (AAP) opposes boxing in any sports program for children and young adults.

Writing in the August issue of *Pediatrics*, the journal of the AAP, the Academy's Committee on Sports Medicine reports recent studies using computerized tomography (CT) scanning have revealed brain injury in young boxers previously missed by EEGs and other preflight medical examinations.

Approximately 15,000 boxers 10-15 years of age are currently registered with the Amateur Athletic Union (AAU) Junior Olympics program and many more may be involved in community organizations.

Ironically, protective headgear may actually increase brain injuries. The sports medicine experts say the degree of physical injury in boxing correlates with the physical strength and activity of the participants.

Pediatricians' opposition to boxing should be expressed to both boxers and the public alike. To help augment that cause, brochures amplifying the dangers of boxing should be made available in pediatric waiting rooms.

AAP News Release- August 13, 1984

PEDIATRIC HEALTH CARE INCENTIVE ACT PROMOTES COST MANAGEMENT, PREVENTIVE CARE

Health insurance is really illness insurance, and runaway costs and sick children are victims of inequitable, tax-supported design.

The "Pediatric Health Care Incentive Tax Act," sponsored by Senator John Chafee (R-RI) would deny tax deductibility to employer group health plans which fail to cover preventive health services to children.

"We applaud Senator Chafee's efforts to end the insurance industry's historic discrimination against children," says Paul F. Wehrle, president of the American Academy of Pediatrics.

Wehrle notes that this measure is consistent with Congress' recent tax initiatives to make the tax system fairer for all segments of society. "We are not proposing that all sniffles and bruises be covered by this plan," says Wehrle. "Only specified services such as appropriate immunizations, and blood and urinalysis tests recommended to detect potentially hazardous illnesses would be covered under this new act."

The cost for this proposed type of pediatric preventive care would amount to about \$2.50 per month per employee in group health plans. This is only one percent of the current costs to employers. Yet, as Dr. Wehrle points out, this incentive act would help reduce unnecessary hospitalization by removing the financial barrier to preventive services children require. To that extent, the

bill would promote positive health supervision while reducing long-term illness costs.

AAP News Release- Division of Communications, June 28, 1984

PEDIATRICIANS CAN HELP IDENTIFY AMERICA'S GIFTED CHILDREN

The highly intelligent child with no access to a gifted student program can become a problem and might even drop out of school, warns the head of a talent identification program.

To help prevent wasting talent and to identify gifted children (top 3 percent of each class), Duke University Professor Robert Sawyer maintains it is a pediatrician's obligation to spot gifted students.

Gifted students should be in places where they get new challenges and can be with other bright kids," says Prof. Sawyer, who spoke to the American Academy of Pediatrics (AAP) at their Annual Meeting.

During the past decade, the outlook for many gifted students has been getting better. "There is a great deal of interest in gifted student programs and we'll continue to see more programs over time. Though there is no present federal policy for the gifted, the government is beginning to focus on these programs," Prof. Sawyer says.

American Academy of Pediatrics News Release: September 18, 1984



AMERICAN COLLEGE OF CARDIOLOGY

PATIENT SELECTION FOR BALLOON ANGIOPLASTY CALLED COMPLEX ISSUE

Selecting patients for balloon angioplasty has always been a critical determinant of success in reperfusing coronary arteries. In applying this technique in multivessel disease, patient selection becomes even more important, according to Ronald E. Vlietstra, M.B., Ch.B., F.A.C.C., associate professor of medicine, Mayo Medical School, Rochester, MN.

From 4 years experience of angioplasty in nearly 200 patients with multivessel disease, Dr. Vlietstra reports that 75 percent of such patients can be treated successfully. Dr. Vlietstra defined several selected subgroups that are excellent candidates for angioplasty with current state-of-the-art technique and equipment, at the original contribution session "Percutaneous Transluminal Coronary Angioplasty—Patient Selection and Results." Results."

"When we talk about patients who are suitable or unsuitable for balloon angioplasty," Dr. Vlietstra says, "we should recognize the anatomic heterogeneity of multivessel disease. Angioplasty is suitable for some and

not for other."

On the one hand, angioplasty works in patients whose multiple blockages are accessible and penetrable. This can be determined, with reasonable certainty, from angiographic studies and clinical information.

On the other hand, if a severe lesion is inaccessible because the vessel is tortuous, or if the occlusion is complete and old (more than 3 months), then the patient is considered less suitable for angioplasty.

Cardiovascular specialists may want to recommend bypass surgery over angioplasty in patients with chronic complete occlusions, he says, because they have the highest rate of complications during balloon angioplasty and their symptoms are least likely to be helped.

The most common complication, which occurs in about 5-10 percent of patients with multivessel disease, is coronary occlusion induced when the balloon catheter is manipulated through the stenosis. This may cause angina in some patients, but in other patients, with reduced collateral flow due to complete occlusion at other sites, acute occlusion has caused transmural infarction and one death.

In their study of almost 200 patients with multi-vessel disease, Dr. Vlietstra and his colleagues has an overall complication rate of about 10 percent; almost all were handled successfully with emergency bypass surgery.

At Mayo Clinic, cardiovascular specialists have been performing balloon angioplasty on patients with multivessel disease increasingly during the last 4 years. Their success rate in these patients approximates that in angioplasty patients with single-vessel disease. The rate of complications is also comparably low.

"The development of PTCA is analogous to that of bypass graft surgery," Dr. Vlietstra says. "In the early experience with bypass grafting, single vessel obstructions were grafted. As surgeon's experience, competence and confidence grew, they began grafting veins across lesions in several vessels. PTCA is now into this same stage of development. Today we see successful attempts to dilate obstructions at several sites. This will increase the use of PTCA by extending its application to other categories of patients."

According to the experience at Mayo Clinic, Dr. Vlietstra estimates this may expand the use of PTCA from about 10 percent to about 20 percent of candidates for bypass grafting. However, he cautions against over-emphasizing the importance of results obtained in a small series of patients. He suggests the need for a randomized, multicenter trial of PTCA compared to bypass surgery for selected patients with multivessel disease to determine the comparable clinical efficacy of these 2 revascularization techniques.

FINDINGS REPORTED ON CLINICAL NMR IMAGING OF THE HEART

"Using gated magnetic resonance imaging (MRI), it is possible to see internal anatomy of the heart without contrast media," says Charles B. Higgins, M.D., F.A.C.C., Professor of Radiology and Director of Clinical

Magnetic Resonance Imaging, University of California School of Medicine, San Francisco.

"These images of the heart are clear and sharp; they show blood within the chamber and the inner wall of the heart," he says. "The images give very sharp definition for measurements of the thickness of the myocardial wall, thereby measuring hypertrophy, for example. Serial images can follow progression or alleviation of hypertrophy by therapy."

These images have been made possible because gating of human heart scans is now done successfully using an electronically isolated ECG system to switch on the NMR scanner at a particular point in the heart cycle. The scanner takes 5 simultaneous scans of 7 mm thickness with a 2 mm gap, so that a 4.5 cm section of the heart can be completed within 4-8 minutes, depending on heart rate.

Magnetic resonance imaging can diagnose many types of heart disease, such as previous MIs, cardiomyopathies, congestive heart failure and several forms of pericardial disease. The technique also can measure severity of these pathologies, such as the size of an infarct.

These magnetic resonance images can show the proximal portion of the coronary arteries, but they do not give any "meaningful diagnostic information" at this time, Dr. Higgins says.

Furthermore, MRI provides the potential for information beyond anatomy. While not yet realized, even in laboratories, investigators are beginning to see early successes in characterizing tissues with MRI. Tissue characterization, as well as the tissue contrast in anatomical images, is based on an elusive property called relaxation times. Depending on the pathology being investigated, a patient may be scanned in one or 2 modes to give images enhanced for relaxation times T_1 or T_2 .

Images of the heart generally are taken in the spin echo mode of a 3.5 kilo Gauss superconducting magnetic scanner. Images can be enriched in T_1 at short repetition rates, for example. When enriched in T_1 or T_2 , images reveal pathologies with different sensitivity.

Researchers have not completely determined the capability of tissue characterization by using relaxation times. More studies need to be done before routine scanning algorithms will be developed for best detecting, characterizing and quantitating various lesions.

"We don't know the best conditions for imaging all pathologies and distinguishing them from normal tissues," Dr. Higgins says. "We get more information all the time. Sometimes, taking an image of a patient is a shot in the dark, whereas, in other patients, we know what image parameters we will use to get the best results."

"We're early in the game," Dr. Higgins continues. "We've done about 120 patients. We're comparing what we find with MRI images to what we see with other imaging techniques such as cineangiography, echocardiography and X-ray CT. Sometimes, MRI gives better images; the initial experience is exciting. But a double blind randomized trial comparing MRI to other techniques has not been done anywhere. We also have not used MRI to do prospective diagnosis of patients with cardiac problems. We've just been using MRI on the heart for about one year."



AMERICAN COLLEGE OF
EMERGENCY PHYSICIANS

CPR - ARE WE TRAINING THE RIGHT PEOPLE?

While mortality rates attributed to coronary heart disease have declined since the mid-1960s, heart attacks continue to be the major cause of death and disability in the United States, causing 300,000 deaths annually.

The majority of heart attack deaths are sudden, unexpected, and occur outside the hospital. According to an article appearing in the September issue of *Annals of Emergency Medicine*, the most effective treatment of sudden death is bystander-initiated cardiopulmonary resuscitation (CPR).

The article reports that up to 12 million Americans have been trained in CPR using the American Heart Association standards, with an additional 50 to 60 million expressing interest in undertaking such training.

"While these efforts are extremely important, limited resources might be more effectively directed at those people most likely to use such skills," says Robert J. Goldberg, PhD, author of the study. "It is important for the family members of patients with known coronary heart disease or survivors of heart attacks to be trained in CPR. It also seems likely that these individuals would be motivated to learn the basic life support skills."

Dr. Goldberg and his colleagues conducted the study to examine the extent of CPR Training among family members of patients with coronary heart disease, family members of patients without coronary heart disease and a random neighborhood control group.

Results of the study indicate that family members of patients with coronary heart disease were significantly older than were family members in the two comparison groups, and fewer of these family members had taken CPR than the remainder of the population studied.

In addition, there were significant differences in the timing of previous CPR courses. Only 9% of family members of patient with coronary heart disease had taken a CPR course within the past three years, while a total of 34% of the other groups had. Furthermore, only 9% of these family members had taken CPR due to their family member's heart attack.

Reports from several communities with large numbers of people trained in basic life support have shown that more than 40% of patients with out-of-hospital heart attacks can be resuscitated successfully with prompt use of CPR.

"Because of the increased risk of coronary heart disease and sudden death in older people, it is of particular importance for these individuals and their immediate families to receive CPR training," Dr. Goldberg explained. "Our study clearly highlights the need for additional CPR training and emergency preparedness among family members of patients with coronary heart disease. Efforts must be made to encourage these family members to seek CPR training."

SOCIOS NUEVOS



ACTIVOS

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Every Woman has a Priceless Gift to Offer her Child... Good Health*

By making your fresh start without cigarettes, you are giving your child a Head Start to life: good health at birth. This is the kind of Head Start you can give your child**.

A 30 per cent better chance of survival in the first days of life.

Greater weight at birth—mothers who do not smoke are far less likely to have an underweight baby than women who smoke during pregnancy.

On average, babies whose mothers do not smoke are about 1.3 centimetres longer than those of smoking mothers.

Children whose mothers did not smoke during pregnancy tend to be



about three to five months ahead in their school work compared to where they would have been had their mothers smoked during pregnancy.

Children of non-smoking mothers, on average, do better in psychological tests than children of women who smoke during pregnancy.

Only you can give your child this Head Start. To smoke throughout pregnancy may mean handicapping your child for at least the first 11 years of life—but even if you only make your Fresh Start two days before your child's birth*** he or she will benefit.

There are no disadvantages to making a Fresh Start.

* From an Australian Heart Foundation pamphlet.

** Information taken from the US Surgeon General's report: Smoking and Health, 1979.

*** British Medical Journal, 11th August 1979.

What can you do for hypertensives like Manuel G?

Controlled

Current medication brought blood pressure from 172/110 to 148/92 mmHg.

Successful

Too preoccupied on business trips to remember his pills.

Family man

Loves kids...his wife would like several more.

Impotent

Blames his current blood pressure medication.



Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Manuel G represents 5,314 men age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Sexual dysfunction rare

Only 0.4% of the patients in the evaluation reported sexual performance problems²—making TENORMIN an excellent choice for men like Manuel G, who may have become impotent on other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Manuel G...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary
of prescribing information.



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN® (atenolol)

For Manuel G...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages, first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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STUART PHARMACEUTICALS

Division of ICI Americas Inc.

Wilmington, DE 19897

STR-2230



CITE HEALTH PROBLEMS FROM NUCLEAR FALLOUT

Two studies in the August 3 issue of JAMA describe cases of bone marrow abnormalities and pituitary tumors related to exposure to fallout from nuclear tests.

In one study, Glyn G. Caldwell, MD, and colleagues, of the Centers for Disease Control in Atlanta, followed 3,217 participants present during the detonation of the nuclear device, "Smoky," in 1957. Two cases of polycythemia vera and two suspected cases were found. The disease is also characterized by increased numbers of leukocytes and platelets and an enlarged spleen. "Only 0.2 cases would be expected in a population of this size during this time period, yet four were observed," the researchers say.

Polycythemia vera has been noted among Japanese exposed to the atomic bomb blasts at Hiroshima, the researchers note, but not among survivors at Nagasaki. Follow-up studies of the 3,217 "Smoky" participants revealed increased frequency of leukemia but not of other malignant neoplasms. The frequency of other, nonmalignant conditions has not been fully examined, the researchers say. They conclude, "The small individual whole-body doses of radiation reported for these four participants makes the association with ionizing radiation tenuous, although this was the only known unusual risk factor."

In a second study, William H. Adams, MD, of Brookhaven National Laboratory, Upton, New York, and colleagues reported on pituitary tumors found in two young women who were exposed to radioactive fallout in the Marshall Islands. The accident occurred in 1954, when a thermonuclear bomb was detonated. Long-term follow-up of that population has revealed a high incidence of thyroid neoplasia and reduced thyroid function.

The researchers compared the incidence rate for pituitary tumors among young women in Olmsted County, Minnesota, from 1971 through 1977 with that of the Marshallese. They found the incidence rate for the Marshallese women in the same age group was 13.6 times higher. For the Minnesota women, the rate was 11 cases per 163,096 person-years, and for the Marshallese women, two cases per 2,176 person-years. The researchers

conclude, "The development of two pituitary tumors in this relatively small population may be evidence that certain types of radiation can induce pituitary neoplasia in humans."

A third article in that JAMA focuses on the use of iodine as a thyroidal blocking agent in the event of a nuclear reactor accident. David V. Becker, MD, of New York Hospital-Cornell Medical Center, and other members of the Environmental Hazards Committee of the American Thyroid Association point out that the radioiodines released could accumulate in unprotected thyroid glands, potentially causing cancer in exposed populations. He suggests that an appropriate dose of potassium iodide may be effective in protecting the thyroid gland if such an accident were to occur.

EXERCISE BENEFITS OLDER MEN AND WOMEN

High-intensity endurance training among older people results in favorable changes in blood cholesterol and in the body's sensitivity to insulin, according to a report in the August 3 issue of JAMA. Both changes are thought to decrease the risk of coronary artery disease and heart attack.

Douglas R. Seals, PhD, and colleagues from the Washington University School of Medicine in St. Louis asked 24 healthy men and women in their 60s (mean age 63) to participate in a 12-month study of the effects of endurance training. Ten served as controls and 14 entered the exercise program, with three dropping out for various reasons before the end of the year.

The exercise program was divided into two six-month periods, the first devoted to low-intensity training (moderately vigorous walking at least three times a week) and the second to high-intensity training (cycling, treadmill walking or jogging). Maximal oxygen uptake increased 12 percent during the first six months and 18 percent during the second. The "total area" for insulin was 8 percent lower during the first period and 23 percent lower during the second.

"Plasma lipid and lipoprotein concentrations were unchanged after low-intensity training, but high-intensity training resulted in an increase in high-density-lipoprotein cholesterol and a reduction in triglycerides (both associated with decreased heart attack risk)," the researchers report.

"It is generally considered that glucose tolerance and sensitivity to insulin deteriorate with age," they add. "However, we have recently shown that this may be true only in sedentary persons....Our findings indicate that although glucose tolerance was unchanged, sensitivity to insulin was substantially improved after 12 months of training in our older subjects." As in diabetes, glucose tolerance is related to development of coronary artery disease.

Commenting on the cholesterol findings, the researchers say, "The most important change observed in our subjects' plasma lipid profile may be the reduction in the

total cholesterol-HDL (high-density-lipoprotein) cholesterol ratio.

"A reduction in this ratio may reflect a lowered risk of developing coronary artery disease," they add. "It appears that exercise training must be intense to elicit these adaptations because triglyceride and HDL-cholesterol concentrations failed to change in response to LI (low-intensity) training."

SERIOUS DEPRESSION MAY LINGER FOR YEARS

As many as 20 percent of patients who suffer a major depressive episode that requires hospitalization may remain seriously ill for two years, according to a report in the August 10 issue of JAMA.

Martin B. Keller, MD, of Massachusetts General Hospital, Boston, and colleagues studied 97 patients who had episodes of major depressive disorder and no history of chronic minor depression. They report that after two years, 20 had not yet recovered. "The rate of recovery was highest in the three months after entry into the study, with a notable decrease in rate after one year," the researchers say. "Most patients who did not recover had severe depressive symptoms throughout the two years of follow-up."

The patients were part of a collaborative depression study who had sought care at inpatient and outpatient psychiatric units in Boston, Chicago, Iowa City, New York City and St. Louis. The researchers found that several factors were associated with serious long-term depression: long duration of the episode before entry into the study, inpatient hospitalization status at entry, intact marriage, low family income, the admitting research center, and a history of nonaffective psychiatric disorders, including alcoholism.

"Patients who are seen considerably after the onset of the episode are at high risk of remaining ill regardless of the other characteristics of their illness," the researchers say. Those who had a nonaffective psychiatric condition that preceded the major episode were also more likely to have a chronic outcome. Although single, divorced, separated or widowed persons have been reported to be more likely to have an episode of depression, the study showed that married subjects had a greater likelihood of long-term depression after a major episode. Age was unrelated to outcome, the researchers observe.

Sixty-four percent of the patients recovered during the first six months, the researchers say, and of those still depressed at six months, only 28 percent were recovered by one year. After that time, the rate of recovery continued to decrease. "We urge general practitioners to recognize the potential chronicity of depressive disorders," the researchers conclude. "Intensive treatment and psychiatric consultation is recommended for patients with depression who do not recover and begin to have a chronic course."

ZINC IN LOW DOSES NO THREAT TO HEALTH

Low doses of zinc added to the diet do not affect lipid or lipoprotein levels in either endurance-trained or sedentary men, according to a report in the August 10 issue of JAMA.

Steven F. Crouse, PhD, of the University of New Mexico, and colleagues base findings on a study including 21 endurance-trained and 23 sedentary men. The men received 50 mg of zinc sulfate or placebo daily for eight weeks. "Despite the fact that plasma zinc increased 15 percent, fasting-plasma high density lipoprotein cholesterol, total cholesterol, low density lipoprotein cholesterol and triglyceride levels did not change in response to zinc ingestion." The researchers say.

"High levels of dietary zinc ingestion have been associated with hypercholesterolemia in rats and have been postulated to contribute to coronary artery disease risk," the researchers add. They note that earlier studies have shown that high doses of zinc (160 mg) lowered the levels of high density lipoprotein cholesterol (thought to be beneficial) in healthy men, which could put them at increased risk for coronary artery disease. The smaller amounts of zinc used in this study did not cause significant changes in lipid-lipoprotein levels in either the trained or sedentary group. "Our results suggest that low-dose zinc supplementation does not put persons at increased cardiovascular risk," the researchers conclude.

The men who the researchers considered endurance-trained ran a minimum of 64 kilometers weekly for at least one month before the study; those who did no regular aerobic exercise were considered sedentary. The researchers found that the men who trained had significantly higher levels of high density lipoprotein cholesterol than the sedentary men.

"The absence of a significant interaction between the zinc dose and training level factors for any of the variables analyzed suggests that zinc was ineffective in altering the lipid profiles of the subjects regardless of physical activity level," the researchers say. "Thus, zinc supplementation, at least in low daily doses, does not negate the beneficial effect of exercise in lipid and lipoprotein concentrations."

The researchers conclude that doses of zinc greater than 100 mg per day, however, should be administered with caution. Doses at that level may increase cardiovascular risk by reducing high density lipoprotein cholesterol levels. A dose of 160 mg is approximately ten times the recommended daily allowance, they point out.

ESTROGEN AND CALCIUM HELP PREVENT OSTEOPOROSIS: NIH

The mainstays of prevention and management of osteoporosis are estrogen and calcium, according to a National Institutes of Health consensus conference report published in the August 10 JAMA. Exercise and nutrition may be important adjuncts, the report adds.

Osteoporosis is an age-related disorder characterized by decreased bone mass, which increases susceptibility to bone fracture. Between 15 million and 20 million people in the United States are affected by the disorder, and some 1.3 million fractures each year are caused by the condition, according to the report.

"Estrogen replacement therapy is highly effective for preventing osteoporosis in women," the report says. "Estrogen reduces bone resorption and retards or halts postmenopausal bone loss."

The report says that case-controlled studies show that women who begin estrogen replacement within a few years after menopause have far fewer hip and wrist fractures than women who do not begin replacement therapy. "Even when started as late as six years after menopause, estrogen prevents further loss of bone mass, but does not restore it to premenopausal levels."

Use of estrogen is not associated with an increased risk of breast cancer but may be associated with endometrial cancer, which "is usually manifested at an early stage and is rarely fatal when managed appropriately." The endometrium is the inner membrane lining of the womb.

"Until more data on risks and benefits are available, physicians and patients may prefer to reserve estrogen (with or without progestogen) therapy for conditions that confer a high risk of osteoporosis, such as the occurrence of premature menopause," the report says.

The report points out that most people do not take the daily recommended intake of calcium of 800 mg, but typically take only between 450 mg and 550 mg. Even the recommended 800 mg per day is too low for postmenopausal women. "It seems likely that an increase in calcium intake to 1,000 to 1,500 mg per day beginning well before the menopause will reduce the incidence of osteoporosis."

NO INCREASED DEFECT RISK FOR VETS' OFFSPRING

Vietnam veterans do not have an increased risk for fathering children with major birth defects, nor do veterans with greater estimated exposure to Agent Orange appear to have an increased risk, according to a new study from Atlanta's Centers for Disease Control.

Writing in the August 17 issue of JAMA, J. David Erickson, DDS, PhD, and colleagues explain that they gained health histories from the parents of a case group of nearly 5,000 babies born with defects and compared them with the histories from parents of a control group of about 3,000 babies born without defects. Both groups were drawn from all the approximately 325,000 births in Atlanta during the years 1968 through 1980. The background risk of serious birth defect in the general population is between 2 percent and 3 percent.

"The conclusion that Vietnam veterans in general have not fathered babies with all type of birth defects combined at higher rates than other men is based on relatively strong evidence," the researchers say.

"In addition, this study does not provide support to the notion that those men who may have been exposed to

Agent Orange in Vietnam have had an increased risk of fathering babies with most types of defects. The conclusion regarding the lack of increased risks associated with Agent Orange is based on considerably weaker evidence than the conclusion about Vietnam veterans in general," they add.

Commenting editorially, Bruce B. Dan, MD, of the AMA, says, "The authors are meticulous in describing the study's background and careful in qualifying their results." Case group and control group were frequency matched to race, year and hospital of birth. Confounding factors, such as maternal age or alcohol use, were considered at length. Indices were drawn to compare a veteran's estimate of exposure to Agent Orange to service history in Vietnam.

"The authors are appropriately cautious in the interpretation of their results, but considering the overall strength of the study, the past evidence from human exposure and the confirming experience of Australian servicemen, it would seem that a fairly strong statement can be made that it is unlikely that serious congenital anomalies in children of men serving in Vietnam were results of that experience," Dan says.

Some 50,000 tons of Agent Orange were used in Vietnam, containing a total of 368 lbs of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) Dan points out. Approximately 2.6 million Americans served in Vietnam. Human exposure to dioxin has been shown to cause a skin condition called chloracne.

"Because serious birth defects occur in approximately 2 percent to 3 percent of all live births, the number of such defects that would be expected to have occurred, to date, in children of Vietnam veterans ranges from 50,000 to 150,000," Dan says. "It is not surprising that a veteran who noted a disturbing skin condition apparently associated with his tenure in Vietnam might question whether a birth defect in his child could also be related to that experience."

The absence of clear cause and effect may be of little consolation to those who have suffered the misfortune associated with birth defects, Dan says. "But perhaps it will encourage us to expend more effort in preventing birth defects in any child."

STUDIES CLEAR VASECTOMY OF LONG-TERM DISEASE RISK

Vasectomy is not associated with any long-term risks of disease, including cardiovascular disease according to two studies reported in the August 24 issue of JAMA.

In one study, Frank J. Massey, Jr., PhD, of the University of California, Los Angeles, and colleagues selected 10,590 vasectomized men from four cities, and paired them with a like number of neighborhood controls who had not undergone vasectomy. Of the total 21,180 men, 20,643 were interviewed from one to 41 years after the operation, with a median follow-up time of 7.9 years. There were ten or more years of follow-up for 2,318 of the pairs.

"Results of this study do not support the suggestions of immunopathological consequences of vasectomy within the period of follow-up," the researchers say. "Except for epididymitis-orchitis [inflammation within the testis], the incidence of diseases for vasectomized men was similar or lower than for their paired controls."

The researchers note that one-half to two-thirds of vasectomized men develop antisperm antibodies, and this may increase their risk of immunologically mediated diseases. This has been observed in studies of animals, which also indicated that vasectomy exacerbated atherosclerosis in mankeys. But in their study, the researchers found no increased risk for immune or endocrine disorders, thrombosis, arthritis, multiple sclerosis, cancer or cardiovascular disease among the vasectomized men.

"Although our investigation was established primarily to detect other immunologic sequelae of vasectomy, extensive information was obtained on cardiovascular disease," the researchers say. "The incidence of overt cardiovascular disease found in this study was less among the vasectomized men than among the nonvasectomized men. This is also true when only deaths from heart disease are considered."

A study reported by the National Institutes of Health in this JAMA also found no evidence of increased risk of coronary heart disease among men with vasectomies. The study was conducted by Edward B. Perrin, PhD, at the Battelle Human Affairs Research Centers in Seattle. Of the nearly 5,000 men in the study, almost 1,400 had had a vasectomy, some for as long as 37 years. The researchers note that the mean time since vasectomy in this group was 15 years, which is the longest period of follow-up to date.

The researchers measured levels of the two most common antibodies to sperm to test the hypothesis that the presence of these antibodies increased the risk of atherosclerosis. The results showed, however, that the men without coronary heart disease were just as likely as those with coronary heart disease to have elevated antibody levels. Smoking, hypertension and family history of coronary heart disease were found to be significant predictors, while vasectomy status was not.

METABOLISM OFFERS KEY TO BENEFITS FROM RUNNING

Metabolism rather than increased caloric intake accounts for the elevation of beneficial blood lipids in runners, according to a new study from Brown University in Providence, R.I.

Writing in the August 24 issue of JAMA, Peter N. Herbert, MD, and colleagues report on a controlled study of runners and sedentary men. Among their findings: runners retained high-density lipoprotein (HDL) cholesterol (considered beneficial in keeping arteries clear of plaque) almost twice as long as sedentary men.

"The mean biologic half-life of HDL proteins was 6.2 days in the runners compared with 3.8 days in the

sedentary men," the researchers say. Furthermore, the mean HDL cholesterol level was 65 mg/dL (milligrams per decaliter) in runners and 41 mg/dL in sedentary men.

The researchers comment, "We found in earlier study that runners consumed 20 percent more calories than sedentary controls and postulated that augmented production of HDL apoproteins might be a consequence of this high caloric intake. However, this study documents that reduced apoprotein catabolism (breakdown into simpler compounds) rather than increased synthesis contributes to the higher HDL levels of endurance athletes."

It is possible that weight loss rather than exercise itself may be responsible for the lipoprotein changes attending endurance training, the researchers say, pointing to other studies that show a HDL-cholesterol rise of 10 mg/dL accompanies a 16-kg (35 lbs) loss of weight.

"We suspect that the effects of exercise and weight loss are at least partially independent, but both may mediate their effects through tissue lipoprotein lipase (enzyme activity involving fatty acids and glycerol in triglycerides)," the researchers conclude.

Lipids are blood substances that serve a number of biological functions, including service as a source of fuel. Lipoproteins are a combination of lipids and protein. High-density lipoproteins contain high levels of protein and relatively little cholesterol. Low-density lipoproteins contain high levels of cholesterol, which is associated with the build-up of atherosclerotic plaque that can block arteries, increasing the risk of heart attack and stroke.

REPORT RADIOTHERAPY CONTROL OF KAPOSI'S SARCOMA

Radiotherapy should be considered the treatment of choice in selected cases of Kaposi's sarcoma in conjunction with acquired immune deficiency syndrome (AIDS), say Jay S. Cooper, MD, and colleagues from NYU Medical Center in New York. In the August 17 issue of JAMA they report on 15 patients so treated. "All tumors exhibited at least partial regression, and the majority responded completely," the researchers say. Chemotherapy typically is used for such patients, but the researchers maintain radiotherapy is preferable.

NEW CLASSIFICATION SYSTEM DESCRIBED

A new international classification system for retinopathy of prematurity is described in the August *Archives of Ophthalmology*. The work of 23 specialists from 11 countries, the new system was deemed necessary "because of modern life-support systems capable of keeping tiny premature infants alive." This and improved ophthalmoscopic techniques have offered new information about the early active stages of retinopathy of prematurity. The new system will contribute to examination and management of infants affected by the condition.

Medicolegal Decisions



PHYSICIAN CLAIMS HOSPITAL VIOLATED ITS BYLAWS IN DENYING HIM PRIVILEGES

Violation of medical staff bylaws may give rise to an action against a hospital, a New York appellate court ruled.

The physician alleged that the hospital failed to follow certain procedures in its bylaws when it denied a physician reappointment to the medical staff. The hospital filed a motion to dismiss because no cause of action was stated.

The court granted the motion. However, the appellate court reversed. New York regulations require hospitals to have a medical staff organized under bylaws approved by the governing board. The regulations state that the hospital bylaws shall include a procedure for granting and withdrawing privileges of physicians and to appeal any such decision. The alleged failure to follow the procedures set forth in the hospital medical staff bylaws does state a cause of action, the court concluded.—*Chalasani v. Neuman*, 468 N.Y.S.2d 672 (N.Y. Sup. Ct., App.Div., Nov. 21, 1983)

PATIENT ALLEGES NEGLIGENCE IN CARE OF VASCULAR DISEASE

A trial court erred in directing a verdict for a physician who was allegedly negligent in treating a patient for peripheral vascular disease, a North Carolina appellate court ruled.

The patient went to his physician on March 25, 1977, for an examination of his left foot because two of his toes turned purple and he experienced pain when he walked. The physician thought he had a bone spur and ordered an X-ray. The X-ray showed the foot to be normal. The patient's toes remained blue and his pain continued for several days after the visit.

The pain and discoloration reappeared in May 1977. He then went to an orthopedic surgeon, who thought the patient had circulatory problems. The patient was referred to a vascular surgeon, who diagnosed a clot or

obstruction in his thigh and popliteal areas of his left leg. The patient was hospitalized, but did not improve.

An arteriogram showed that two of the three blood vessels in his lower leg had clotted off. The surgeon performed a vein bypass operation, but the bypass vein clotted off. He replaced it with a synthetic vein, but it also clotted and gangrenous changes appeared. He finally had to amputate the leg below the knee. A trial court granted a directed verdict in favor of the patient's family physician.

On appeal, the appellate court reversed the decision. The evidence was sufficient to establish that the physician breached the standard of care. A jury could have found that if the physician had properly diagnosed the patient's circulatory condition or referred him to a vascular surgeon earlier, there was a possibility that his leg could have been saved.—*Mashburn v. Hedrick*, 305 S.E.2d 61 (N.C.Ct. of App., Aug. 2, 1983)

NEW TRIAL FOR CLAIM OF NEGLIGENCE IN TREATMENT OF KNEE

A trial court committed reversible error in refusing to instruct a jury on *res ipsa loquitur* in an action arising out of an unsuccessful Hauser knee operation, an Illinois appellate court ruled.

The patient injured her knee in a downhill skiing accident in January 1971. She was treated by an orthopedic surgeon. Conservative treatment failed to alleviate her condition, so he performed a Hauser procedure on June 22, 1971. When that operation did not achieve the desired result, he performed a second one about three months later. The second operation was also unsuccessful, and the patient claimed her knee was left in worse condition than it had been before the operations.

She filed an action against the orthopedic surgeon and his employer. She claimed lack of informed consent to the first operation, which was primarily performed by a first-year resident at the hospital, lack of informed consent to the second operation, and that the doctrine of *res ipsa loquitur* applied. A jury returned a verdict in favor of the physician, and the patient appealed.

On appeal, the court said that the theory of lack of informed consent did not apply where the patient had consented to the procedure but it was performed by someone else. The court said the proper cause of action was battery. The patient had withdrawn her claim based on battery and chose to rely solely on the wrong theory of informed consent.

The court said that the patient's informed consent

claim based on the second operation should also fail. The surgeon allegedly did not tell her that a patellectomy was an alternate treatment to a second Hauser procedure, or that she had osteoporosis. Nevertheless, there was no testimony by the patient on what she would have done if she had been given the additional information. The question was properly resolved by the jury, the court said.

The patient presented undisputed testimony that prior to the first operation she had a lateral dislocation of her patella but afterwards she had a medial dislocation. Her expert witness testified that a secondary medial dislocation was a rare and unusual occurrence. There was also evidence that the surgeon admitted to the patient that he made a mistake and moved the knee "a quarter of an inch too far." The court said that the result of the first Hauser surgery ordinarily would not have occurred without negligence.

The court said the trial court erred in dismissing the *res ipsa loquitur* portion of the complaint and remanded it for a new trial.—*Guebard v. Jabaay*, 452 N.E.2d 751 (Ill. App.Ct., Aug. 3, 1983)

WRONGFUL DEATH STATUTE OF LIMITATIONS APPLIES IN SUIT FOR ANEURYSM PATIENT'S DEATH

A medical malpractice action was governed by the statute of limitations for wrongful death actions, a Georgia appellate court ruled.

A patient died of an aneurysm that was not detected on an X-ray. His widow filed a wrongful death action against the physician who read the X-ray. The appellate court said that the medical malpractice limitations statute, which began to run on the date of malpractice, applied to the widow's claim.

The Supreme Court overruled the decision and remanded the case to the appellate court. On remand, the court said that the appropriate statute of limitations was the wrongful death statute, which ran for two years from the date of death. The court said that in cases where medical malpractice led to death the wrongful death statute, not the malpractice limitations period, was the appropriate limitations period.—*Hart v. Eldridge*, 306 S.E.2d 98 (Ga.Ct. of App., April 28, 1983; rehearing denied, May 26, 1983)

MALPRACTICE SUIT BY FRACTURE PATIENT NOT BARRED BY TIME LIMIT

A patient's suit, filed within one year of discovery of alleged negligence, was not barred by the statute of limitations, the Tennessee Supreme Court ruled.

The patient fell at home on November 29, 1979, fracturing three bones in her foot. The next day, she was examined by a physician at a hospital emergency room. He consulted a radiologist to review the patient's X-rays, and then told the patient she had no broken bones but only a tendon sprain. In December, 1979, a local

orthopedic surgeon advised her that she could walk on her injured foot. She allegedly did not discover that the bones were broken until she visited her daughter in another city and another X-ray was taken, on March 11, 1980.

On March 10, 1981, within one year after discovering her injury, but almost 16 months after the alleged malpractice occurred, the patient filed a malpractice action. The physicians moved to dismiss, relying on the one-year statute of limitations. On interlocutory appeal, the court held that the cause of action was barred by the statute of limitations.

On appeal, the Supreme Court said that where an alleged injury was not discovered within the one-year period, the statute of limitations was one-year from the date of discovery, with a three-year ceiling on the date of discovery rule. Where the patient filed her complaint on March 10, 1981, after discovering her injury on March 11, 1980, the court found that it was timely filed. The court reversed the judgment of the appellate court and sent the case back for trial.—*Hoffman v. Hospital Affiliates, Inc.*, 652 S.W.2d 341 (Tenn.Sup.Ct., June 6, 1983)

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Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

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El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

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Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

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Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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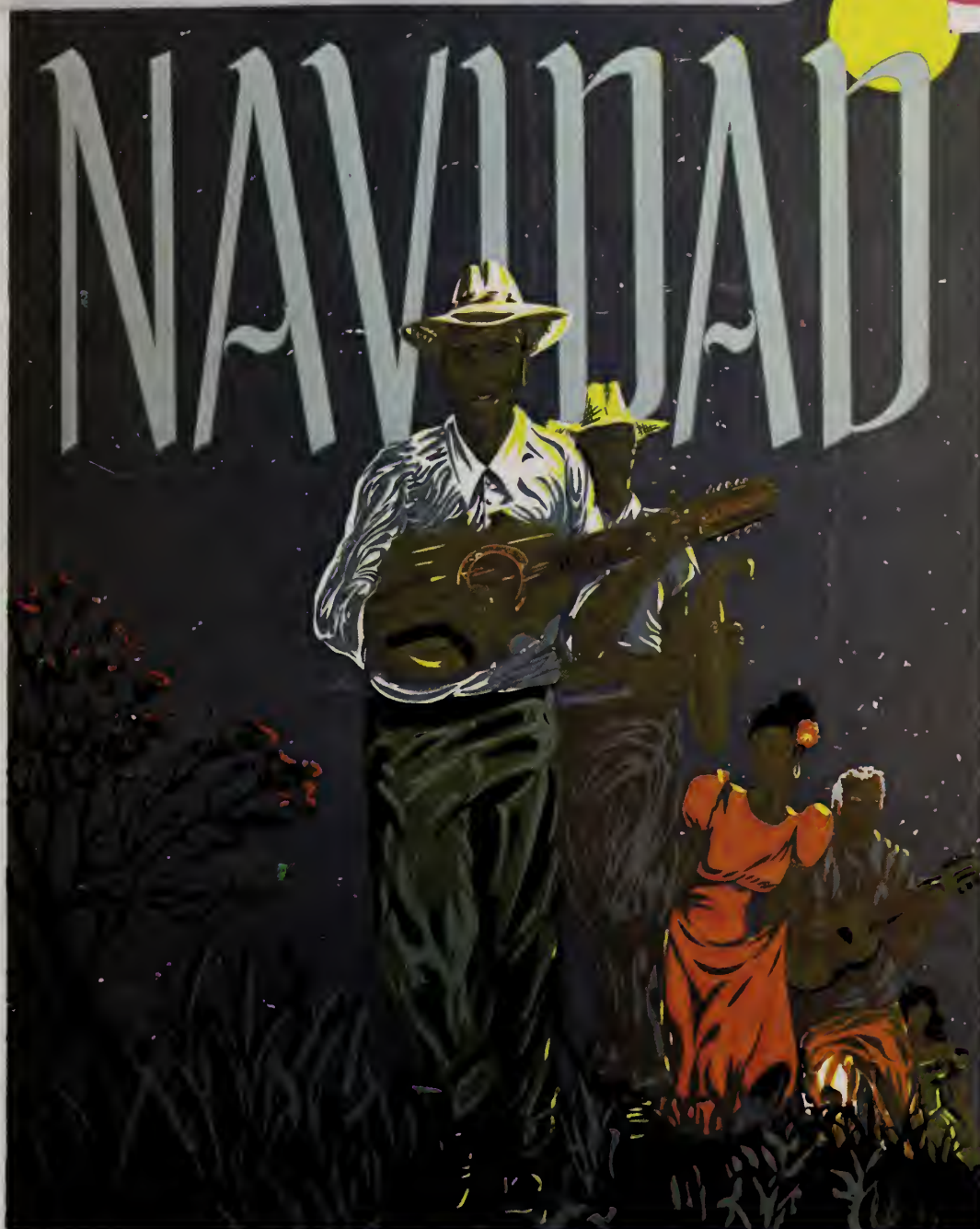
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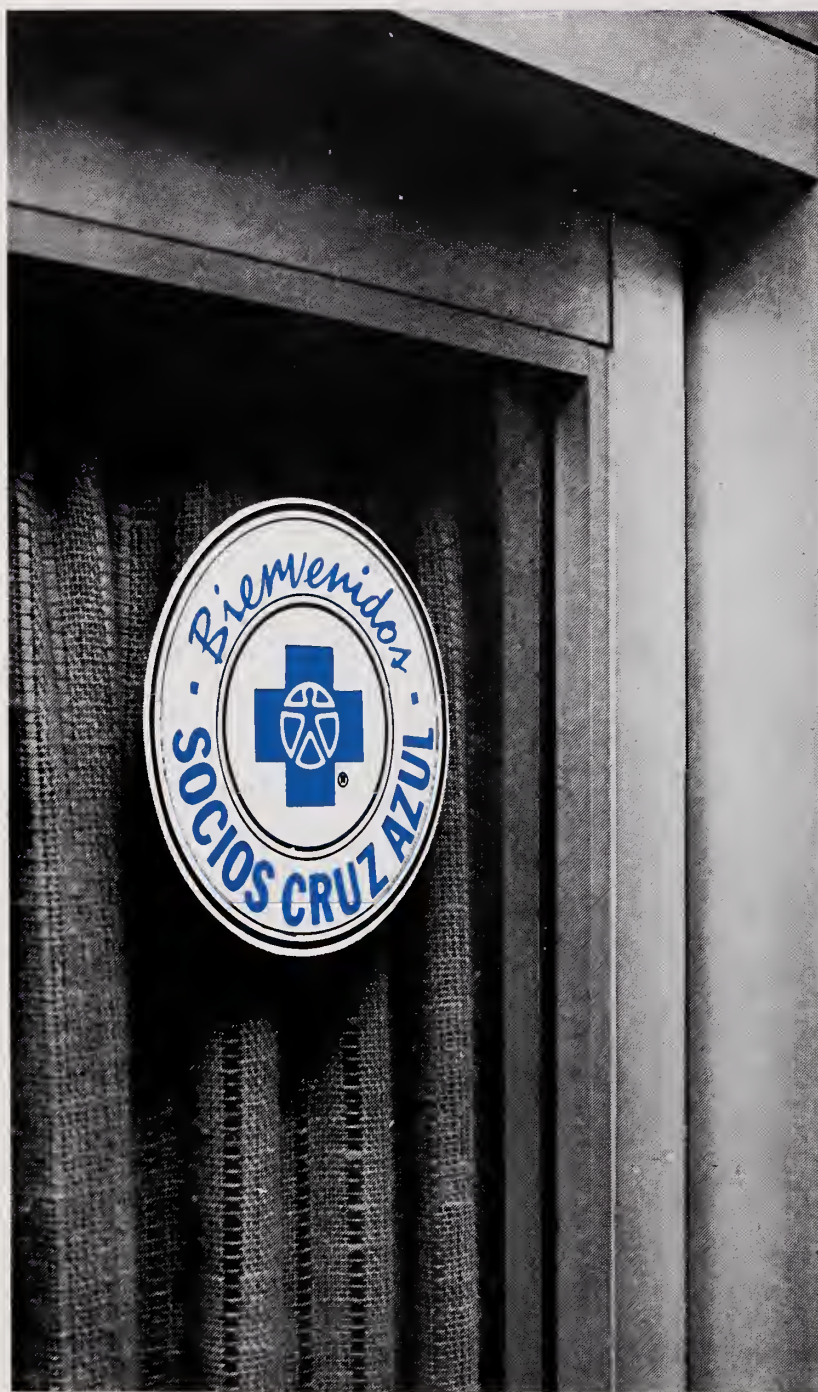


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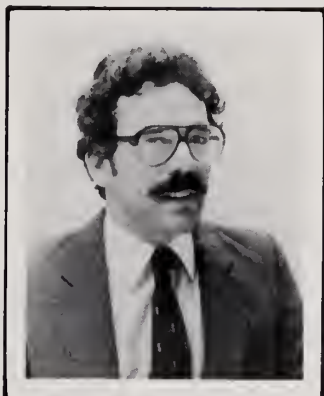
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Columna del Editor



Es este el último número del volumen 76 de nuestra revista y el número treinta y seis preparado por esta Junta Editora con el nuevo formato. Su portada refleja el espíritu festivo de la época navideña tan arraigado en nuestro pueblo. Es un mensaje de alegría que queremos transmitir a nuestros lectores luego de un año de tanta discordia nacional a todos los niveles. Cuando se termina con alegría, la tristeza, tribulación o pesadumbre inicial es menos difícil de olvidar y el optimismo renace de forma natural.

El contenido de la revista refleja nuestros objetivos editoriales: artículos de calidad científica preparados por expertos en el tema, abundante experiencia local con fines didácticos y prácticos, así como artículos de repaso y noticias de las especialidades médicas.

La Junta Editora desea enfatizar su interés en la publicación de artículos que representen la "experiencia nacional" y exhorta a los autores con trabajos de este tipo que los sometan para nuestra consideración. Es pertinente recordar que para su publicación debe cumplirse con las normas que aparecen en las Instrucciones a los Autores y que todo trabajo debe pasar por el proceso de arbitraje.

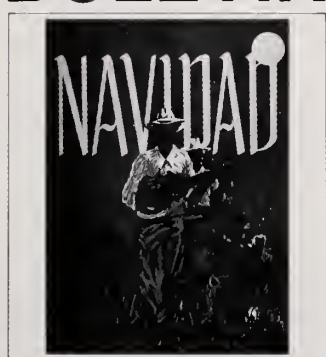
La Junta Editora de 1984 quiere por este medio agradecer las buenas intenciones de todos aquellos que tuvieron frases de elogio para nuestra revista, estas ayudaron a que cumpliésemos nuestro cometido. También tienen su mérito los que se encargaron de criticarnos, pues fueron ellos el mejor estímulo para lograr nuestra superación editorial.

Mucha salud, éxito y mejores intenciones para 1985 les desea la Junta Editora del Boletín de la Asociación Médica de Puerto Rico a todos nuestros lectores.

Rafael Villavicencio, MD, FACC
Presidente Junta Editora
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ASOCIACION MEDICA DE PUERTO RICO

BOLETIN



VOL. 76 / NUM. 12 DICIEMBRE 1984

NUESTRA PORTADA

Epoca de Navidad. Cartel del artista puertorriqueño Rudy Morciglio. Este cartel fue preparado por el autor hace varios años en el taller de artes gráficas de la División de Educación a la Comunidad del Departamento de Instrucción Pública (DIVEDCO). Nos informa el Sr. Tony Maldonado, reconocido artista puertorriqueño y director de la Sección de Artes Gráficas de DIVEDCO, que el joven Morciglio es oriundo de la ciudad de Yauco de padres puertorriqueños y llegó a DIVEDCO de la ciudad de Nueva York. En su breve pasantía por los talleres de DIVEDCO mostró su habilidad artística en la preparación de carteles para las actividades educativas auspiciadas por esta agencia gubernamental.

La Junta Editora basó la selección de su portada no solamente por la estampa típica que ilustra sino también por la sensación de alegría y espíritu festivo de nuestra gente que logra reflejar el artista en su obra.



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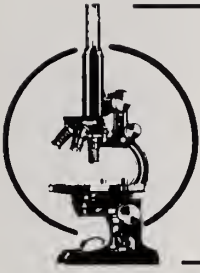
La Junta Editora del Boletín de la Asociación Médica de Puerto Rico para el 1984 quiere al finalizar el año testimoniar su agradecimiento a una serie de personas que nos brindaron en todo momento su valiosa cooperación y desinteresada ayuda.

Algunos realizaron la difícil labor de evaluar los trabajos sometidos para publicación, otros proveyendo asesoramiento y algunos supliendo material gráfico y científico de interés.

El Boletín ha tenido un año exitoso, las metas propuestas fueron alcanzadas y superadas; nuestra revista dejó beneficios a la Asociación Médica por primera vez en su historia; recibimos felicitaciones nacionales y del exterior y sobretodo nuestra matrícula ha manifestado su agrado unánime. La ayuda de estas personas permitió esto se lograra. A todas ellas nuestras mas sinceras gracias y profundo agradecimiento.

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PATHOLOGY *Review*

María Castillo Staab, M.D.

Una mujer de 50 años de edad es admitida al hospital con historial de dolor abdominal, aumento del tamaño del abdomen, náusea y disuria.

El examen físico reveló la presencia de una masa pélvica ocupando el área del anejo izquierdo. La sigmoidoscopia y la enema de bario fueron reportadas negativas.

La paciente fue operada cuatro días después y se encontró la lesión representada en la figura 1.



Figura 1. Masa pélvica extirpada.

El diagnóstico más probable es:

- a) Diverticulitis del colon sigmoide
- b) Tumor de Brenner
- c) Carcinoma de la vejiga urinaria
- d) Cistadenocarcinoma mucinoso del ovario
- e) Disgerminoma

Cistadenocarcinoma Mucinoso del Ovario

Es un tumor maligno del ovario originado del epitelio celómico de revestimiento del cual se derivan el epitelio de las trompas de falopio, el endometrio, el endocuello y el epitelio escamoso del ectocervix y la vagina. Los tumores mucinosos representan el 20% de todos los tumores malignos del ovario. Los cistadenocarcinomas serosos representan la mayoría con un 50%, seguidos de los de tipo endometriales y los no diferenciados. El carcinoma de ovario de origen epitelial tiende a ocurrir en mujeres entre los 40 y 70 años de edad. Es más común en mujeres de países industrializados aunque su incidencia es bien baja en las mujeres del Japón. Hemos notado un aumento progresivo en el número de casos de carcinoma de ovario en los últimos veinte años, tumor que ocurre con más frecuencia en nulíparas y mujeres de pocos embarazos.



Figura 2. Tinte de mucicarmina

Clínicamente los signos y síntomas iniciales son inespecíficos. Más tarde el paciente desarrolla dolor abdominal, aumento del tamaño del abdomen, masa pélvica y ascitis. Algunas pacientes pueden presentar sangramiento vaginal anormal.

El examen pélvico es el mejor método para evaluar la presencia de un posible tumor de ovario.

El hallazgo de una masa fija en el área de los anejos debe hacer sospechar al examinador que la lesión es maligna. Tumores y masas de más de 5 cm de diámetro en mujeres perimenopáusicas o que han pasado la edad reproductiva deben estudiarse con sonografía o cirugía exploratoria para descartar la posibilidad de una lesión maligna.

Los tumores malignos mucinosos del tipo de cistadenocarcinoma tienden a ser unilaterales contrario a los serosos los cuales son bilaterales en un 30% de los casos. Macroscópicamente son tumores grandes, multiloculados, con grandes masas quísticas que pueden llegar a pesar varias libras. Los quistes contienen abundante material gelatinoso mucinoso el cual en ocasiones al romperse pueden producir una condición clínica llamada pseudo-

mixoma peritoneal que representa diseminación maligna intra-abdominal.

Microscópicamente el epitelio de estos tumores se parece mucho al epitelio del endocuello. Consiste la lesión de espacios glandulares tapizados por una hilera de células uniformes columnares de núcleo basal conteniendo vacuolas de moco (Fig. 2). A veces este epitelio se parece mucho al epitelio del intestino y del estómago e histológicamente puede resultar difícil para el patólogo decidir en lesiones metastáticas cual es el origen del tumor.

En el diagnóstico patológico de los tumores de ovario es importante recordar que además del valor pronóstico del tipo histológico de la lesión (seroso, mucinoso, endometrial, etc.) debe reportarse también el grado de diferenciación celular, o sea, cuan bien diferenciado o anaplástico es el tumor. Sin embargo el factor pronóstico

más importante al evaluar la sobrevida sigue siendo el estadio clínico de la enfermedad al momento de diagnosticarse la lesión.

Los tumores malignos epiteliales del ovario se diseminan por continuidad, implantación peritoneal y vía linfática. Las metástasis ocurren primero al peritoneo, omentum, diafragma, serosa de los intestinos y nódulos linfáticos. Ocurren también al útero, ovario contralateral, hígado, pleura, etc.

El manejo de pacientes con carcinoma de ovario es básicamente quirúrgico. Dependiendo del estadio de la enfermedad y otros parámetros se utilizan la radioterapia y la quimioterapia en el tratamiento de los mismos.

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Foro de Medicina Nuclear

Bone Scan in Legg-Calve-Perthes' Disease

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F. Silva de Roldán, M.D.

Case Summary

A seven years old white male was in good state of health until April 1983 when he began with left leg pain and limping. There was no history of trauma nor of any other associated illness. Physical examination done by his pediatrician disclosed a painful left hip with limitation of movement, but no evidence of increased heat, swelling or redness.

Roentgenographic evaluation of the pelvis was found negative and an analgesic was prescribed. In spite of this, symptoms continued, and on November 1983 he was referred to an orthopedic surgeon for evaluation. A bone scan was then performed (Figs. 1 & 2) revealing changes in the left femoral head suggestive of Legg-Calvé-Perthes' disease. Subsequent X-rays disclosed changes of avascular necrosis of left femoral head. The patient was then admitted to the University Pediatric Hospital and was treated with traction for two weeks. Since then, he has been using orthopedic braces. Follow up bone scan was done 6 months later (Fig. 3).

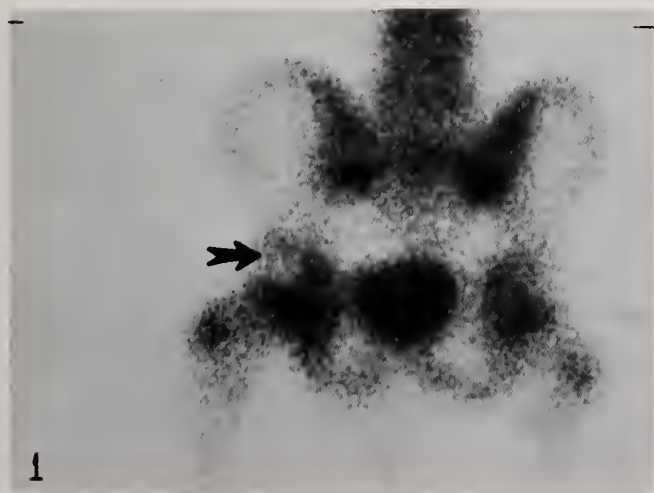


Figure 1. Posterior pelvis image of the bone scan done with ^{99m}Tc medronate revealing the typical photon deficient area in the lateral third of the femoral capital epiphysis (arrow).

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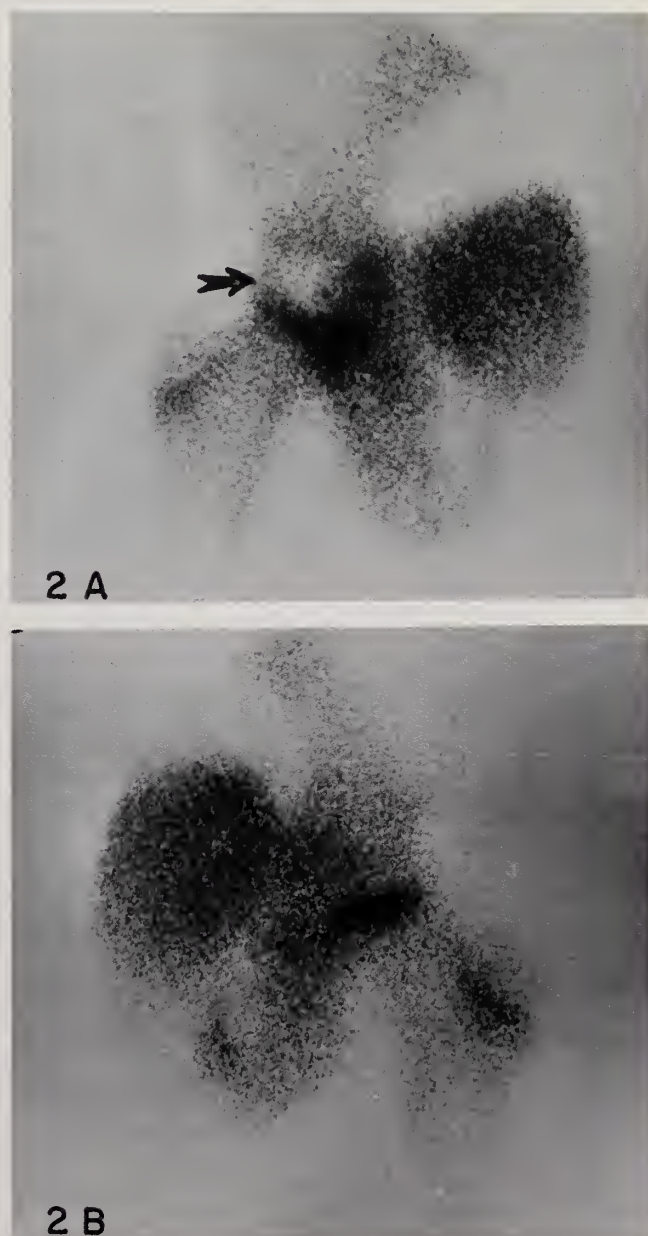


Figure 2. a, b, Pinhole (magnified) views of the femoral heads showing the defect on left side in more detail (arrow).

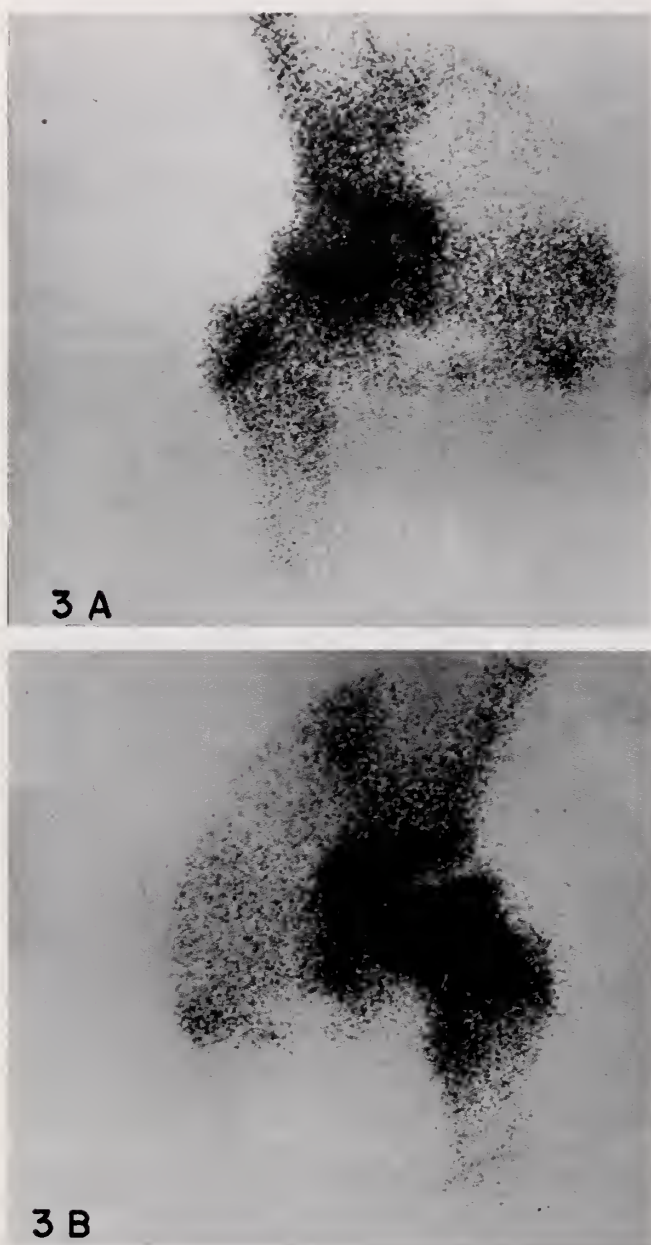


Figure 3. a, b, Follow up study done 6 months later on anterior view (pinhole images) showing a smaller defect due to partial revascularization of the femoral capital epiphysis.

Discussion

Legg-Calvé-Perthes' disease is a self limiting condition seen in the pediatric population, usually between the ages of 3 to 13 years, with a male to female ratio of 5:1.¹ Vascular occlusion, alterations in blood coagulability and a relative insufficient blood supply to the growing epiphysis have been proposed as possible etiologic factors.² The lesion is characterized pathologically by infarction, necrosis and subsequent revascularization of the growing epiphysis.^{3, 4} Clinically, patients frequently present with limping, hip pain or both. Most cases have a good prognosis even when no treatment is given; however, some may progress to deformity of the femoral head and eventual osteoarthritis.

The clinical diagnosis of Perthes' disease is difficult, and frequently has to rely on history, physical examination and roentgenographic findings.⁵ Radiography provides satisfactory information about bone contour and density, but little insight as to the functional status. In the early stages of the disease they are usually normal. As the disease evolves, flattening, broadening, irregularity and sclerosis of the femoral head can be seen on X-rays. Bone death does not produce immediate changes in the radiographic density. Radionuclide imaging, on the other hand, can be used to establish an early diagnosis of bone necrosis. The degree of tracer uptake is primarily a function of the blood supply to the bone and may thus be used to identify areas with alterations in perfusion.³ The scintigraphic appearance of Perthes' disease in the early stages is initially characterized by an area devoid of activity in the femoral capital epiphysis which can be easily distinguished from the normal capital epiphysis. There is increased activity in the acetabular region because of an associated synovitis. The initial size of the epiphysal defects correlates well with the degree of impaired blood supply.² The sensitivity of bone imaging to reliably diagnose Perthes' disease is 98%, and the specificity is 95%, while plain radiograph has a 92% sensitivity and 78% specificity. False positive studies have been described with conditions that impinge upon the vascular supply to bone, such as tumor, sickle cell disease, trauma, and steroid therapy.⁶

Computer quantitative analyses of the femoral head can increase the sensitivity of the procedure and provide a more accurate follow up procedure.⁷ Revascularization of the femoral capital epiphysis represented by the increase in activity in the affected hip on serial studies can also be recognized earlier with radionuclide imaging.

In summary, bone scan has proved to be the most sensitive non invasive study in the early diagnosis and follow up of Perthes' disease.

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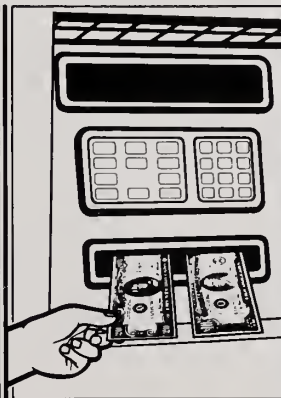
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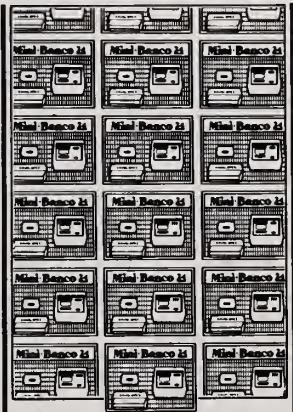
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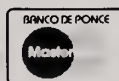
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What can you do for hypertensives like Janet M?

"Scared" of doctors

But insurance physical reveals a diastolic of 104 mmHg.

Career woman

At her peak at 50...no room in her busy schedule for a complicated regimen.

Eats out

Will try from now on to select dishes with fewer calories.

Childhood asthmatic

Hasn't wheezed in forty years.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Janet M represents 4,533 women age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol use has been associated with bronchospasm even in patients with no history of wheezing or dyspnea.³ Unlike propranolol, TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors.⁴ Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



**For Janet M...and virtually
all your hypertensive patients**

ONE TABLET A DAY
TENORMIN[®]
(atenolol)



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN® (atenolol)

For Janet M...
and virtually
all your
hypertensive
patients



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol) with caution—see OVERDOSAGE. Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1–2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.5%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects (TENORMIN (atenolol)).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotensive bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet daily either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100–150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15–35	16–27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 10 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Clinical Spectrum and Surgical Management of Anomalous Origin of the Left Coronary Artery from the Pulmonary Trunk.

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S. Subramanian, M.D., F.R.C.S., F.A.C.C.**

Summary: An anomalous left coronary artery arising from the pulmonary artery is an uncommon congenital anomaly which carries a serious prognosis with a high mortality. Our experience in the surgical treatment of 9 patients with this condition is discussed. The majority of patients were under the age of 2 years and presented with left ventricular failure. Surgical procedures included simple ligation of the left coronary artery, left subclavian to left coronary artery anastomosis, interposition vein graft, and direct reimplantation of the left coronary artery into the aorta. Patients treated by simple ligation survived the procedure but did not show improvement. Results with the subclavian artery to left coronary artery anastomosis were disappointing. Small size of the saphenous vein in infants was a limiting factor for interposition graft. Direct reimplantation appears to be the method of choice.

An anomalous left coronary artery arising from the pulmonary artery is an unusual congenital cardiac

anomaly with over 200 reported cases.^{2, 15, 20} This anomaly carries a serious prognosis with mortality of 80-90% in infants.^{11, 20} Approximately 15% of cases survive beyond infancy. In some cases survival up to the middle age is possible depending upon the development of intercoronary anastomotic channels.²⁰ Proper therapy of this condition is still controversial.^{2, 14} We present our surgical experience with 9 patients seen at the Children's Hospital of Buffalo and discuss the evolution of current surgical management.

Clinical Material and Methods

From January 1975 to December 1979, 9 patients underwent operative treatment for the anomalous origin of the left coronary artery from the pulmonary artery. Table 1 shows preoperative patient data. Ages ranged from 9 weeks to 11 years. There were 7 female and 2 male patients (F:M ratio 3:1). The majority of the patients

TABLE I
PREOPERATIVE PATIENT DATA

Patient	Sex	Age	ECG Features	LVEDP in mmHg	SVC	RA	Oximetry RV	MPA	Qs	Scintigraphic Features
1	F	4 mos.	T wave inversion in Lead I, AVL, V5, V6	9	68%	62%	62%	75%	1:1	Tc99m pyrophosphate scan: diffuse uptake in the entire left ventricle suggesting ischemia
2	F	10 mos.	Deep Q wave in I, AVL, and T wave inversion V5, V6, AVL, V5, V6	12	59%	65%	62%	72%	1:1	Tc99m pyrophosphate myocardial scan: diffuse increase in uptake in the region of LV indicating ischemia. Thallium 201 scan: absent deposition at the apex of the left ventricle
3	F	21 mos.	Deep Q wave in I, AVL, V5, V6	20	--	--	--	--	*	Tc99m pyrophosphate scan: extensive deposition in the left ventricle, severe ischemia of left ventricle
4	F	7 mos.	Q wave in Lead I, AVL, V6, V7	7	56%	55%	56%	63%	1:2:1	Tc99m pyrophosphate myocardial scan: minimal ischemia
5	F	11 mos.	LVH, LAD	27	65%	58%	51%	55%	1:1	
6	F	2 mos.	Deep Q in I, AVL, V5, V6 T wave inversion in I, II, AVL, V5, V6, ST depression Lead II	8	75%	70%	71%	68%	1:1	
7	F	17 mos.	LVH, LV strain, Flat T wave in V5, V6	10	65%	59%	58%	61%	---	Thallium 201 myocardial scan: normal findings
8	M	11 yrs.	Normal ECG	8	--	--	--	--	*	Thallium 201 myocardial scan: normal findings
9	M	8 yrs.	Normal ECG	6	82%	74%	71%	85%		Thallium 201 myocardial scan: normal findings

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(77%) were under the age of 2 years. The classical symptoms of infantile angina¹ were the presenting complaints in only one infant. The other 6 infants presented with left ventricular failure. Physical examination revealed a systolic murmur in 5 infants. Electrocardiographic changes including signs of infarction, ischemia or left ventricular hypertrophy were present in all patients except 2 asymptomatic older children. Scintigraphic evaluation of ventricular myocardium was performed with Technetium 99m pyrophosphate in 4 patients and with Thallium-201 in 4 patients. Four infants showed left ventricular dysfunction due to myocardial ischemia. Cardiac catheterization and aortogram were performed in all patients (Fig. 1a and 1b).

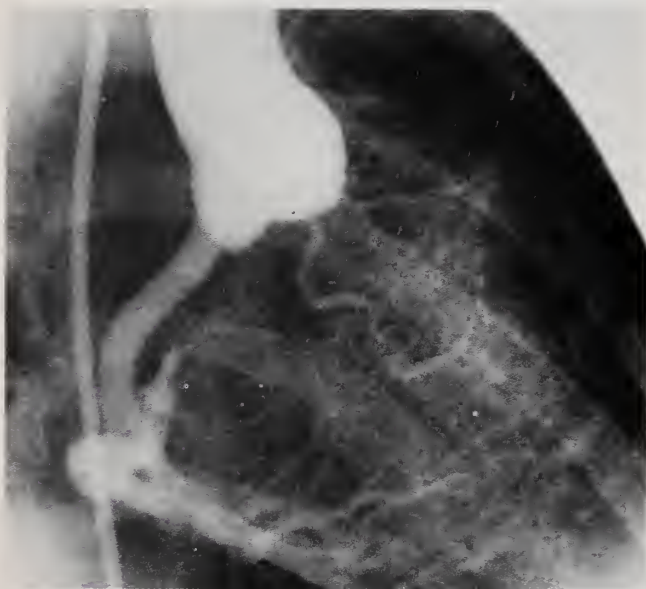


Fig. 1a. Injection of contrast medium into the aorta shows opacification of a large right coronary artery. No left coronary is opacified.

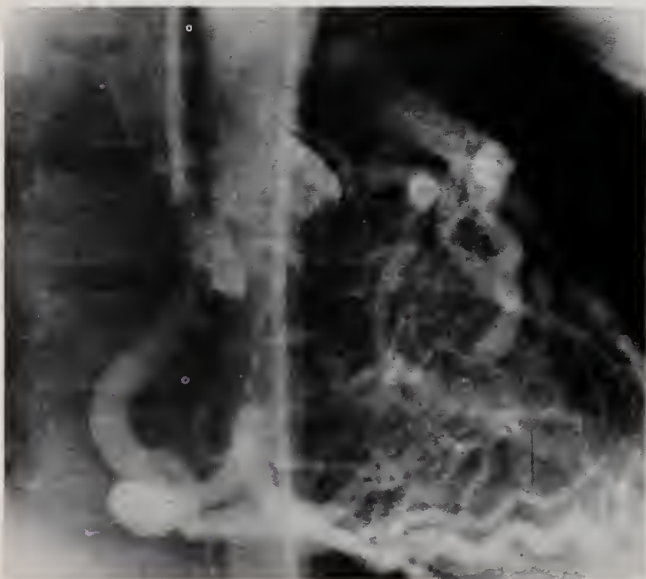


Fig. 1b. One second later - retrograde filling of the left coronary artery by the collaterals from the right coronary. A faint opacification of the pulmonary artery is also seen.

Surgical Management and Results

Surgical techniques employed and the results are shown in Table 2. In the first two infants in this series, the left coronary artery was ligated to prevent a left to right shunt which was well tolerated but postoperatively there was no clinical improvement. In the next 4 patients, the left subclavian artery was anastomosed to the left coronary artery. The anastomosis was performed on a beating heart without cardiopulmonary bypass in 2 infants, both of these patients showed anastomotic occlusion within one month and one of them died. In 2 other infants, the anastomosis between the left subclavian artery and the left coronary artery was performed under surface-induced deep hypothermia and circulatory arrest. Both infants died due to low cardiac output. Autopsy revealed patent anastomoses in both patients.

In one infant, an interposition saphenous vein homograft (Fig. 2) from the patient's brother was used and this resulted in improvement of left ventricular function. This graft remained patent for 8 years when it needed replacement by patient's own saphenous vein (Fig. 4). Direct reimplantation of the left coronary artery into the aorta (Fig. 3a and Fig. 3b) was performed in an 8 year old patient, and another 11 year old patient was treated by interposition with autogenous saphenous vein in end to end fashion. Postoperative angiogram showed satisfactory growth of the reimplanted coronary artery and patency of the saphenous vein graft (Figs. 4 and 5).



Fig. 2. Diagram showing saphenous vein interposition graft for anomalous left coronary artery.

TABLE II
OPERATIVE TECHNIQUE AND RESULTS

Patient	Operative Procedure	Results	Postop. catheterization	Autopsy
1	Ligation of LCA	Poor	---	---
2	Ligation of LCA	Fair	---	---
3	Ligation and LSC-LCA anastomosis without CBP	Expired	Anastomosis occluded 3 weeks after surgery	Extensive MI myocardial fibrosis
4	Division of LCA and LSC-LCA	Fair	Occlusion of anastomosis at 2 weeks after surgery	
5	Division of LCA and LSC-LCA anastomosis and MVR with circulatory arrest	Expired due to postop. low cardiac output	--	Open anastomosis, extensive fibrosis of myocardium
6	Division of LCA and LSC anastomosis with circulatory arrest	Expired on table	--	Open anastomosis, extensive fibrosis
7	Division LCA, interposition of saphenous vein homograft	Excellent	Improved LV function, functioning graft. Re graft 8 years later.	---
8	Division LCA, interposition of saphenous vein autograft	Excellent	Functioning graft	
9	Reimplantation of LCA	Excellent	Normal growth of LCA	

LCA - left coronary artery
LSC - left subclavian artery
MVR - mitral valve replacement

LV - left ventricle
MI - myocardial infarction
CPB - cardiopulmonary bypass

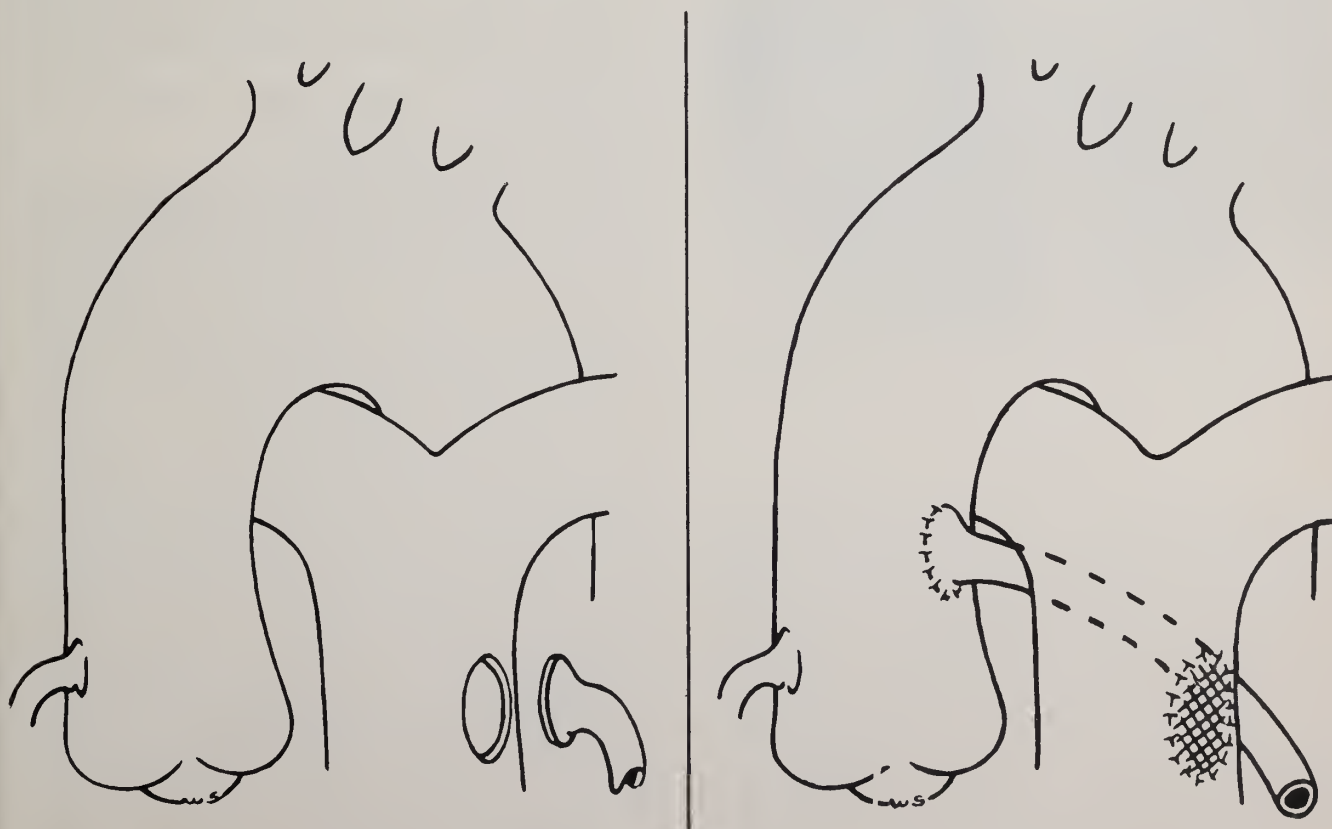


Fig. 3a and 3b. Diagram showing method of direct reimplantation of the left coronary artery into the aorta.



Fig. 4. Aortogram showing a patent saphenous vein interposition graft of the left coronary artery.



Fig. 5. Two year post operative aortogram showing normal growth of the reimplanted left coronary artery into the aorta.

Discussion

Origin of the left coronary artery arising from the pulmonary trunk is the commonest congenital coronary artery anomaly. It was first reported by Brooks in 1885.⁴ Since then, over 200 cases have been reported.^{2, 14, 15, 20} It is potentially a lethal malformation with an 89% mortality in the first year of life.²⁰ Those who survive to their teens and adulthood occasionally die suddenly without preceding symptoms.¹⁰ Its pathophysiology, hemodynamics, surgical treatment and prognosis have been reviewed by several authors.^{2, 11, 12, 20} The alterations in hemodynamics is variable. It was initially believed that the blood flows from the normal coronary originating in the aorta through collateral vessels into the left coronary artery and drain into the pulmonary artery.

It is now clear that this is dependent upon the degree of the development of intercoronary collaterals. In the case of minimal or no collateral development, there is no left to right shunt and the flow is forward from the pulmonary artery to the coronary artery and the myocardium. In moderate collateral development, the left to right shunt is only detectable by angiography but not by oximetry but in profuse collaterals, the left to right shunt is apparent by oxygen step up in the pulmonary artery. Patients in the well developed collaterals are classified as "adult" type and with no collateral "infantile" type¹ but these functional states actually represent different stages of development of the collaterals.⁶ In the infantile type, the anomalous left coronary is supplied by the relatively high pulmonary artery pressure, perfusing the left ventricle poorly due to inadequate collateral circulation. These infants rapidly develop myocardial ischemia and congestive heart failure and most die during the first 8 to 10 months of life. After establishment of adequate collateral vessels (adult type), the anomalous left coronary artery carries blood retrograde into the pulmonary artery forming a left to right shunt. Thus, the clinical manifestation and functional state of a patient with this anomaly would be a dynamically changing phenomenon depending upon the direction of the shunt and the collateral circulation.

Several surgical modalities have been reported for management of this anomaly:

- a) Simple ligation or division of the left coronary artery.^{16, 17}
- b) Anastomosis of the left subclavian artery to the left coronary artery.¹⁸
- c) Direct reimplantation of the left coronary artery into the aorta.^{8, 12, 13}
- d) Saphenous vein graft either by interposition or bypass technique.^{5, 7, 12, 19}
- e) Intrapulmonary rerouting.⁹

There are case reports on success or failure after simple ligation of left coronary artery.^{16, 17} This appears to be related to the state of collateral circulation and the degree and type of shunt at the time of surgery. However, rendering these patients to a single coronary system is not an ideal method of repair, although some patients with significant left to right shunt or coronary steal phenomenon²¹ will show clinical and hemodynamic improvement. Early in our series, this technique was utilized in 2 patients without significant clinical improvement. We have abandoned ligation and now use some type of reconstruction technique. Our experience in subclavian to the left coronary artery anastomosis was disappointing. Although this technique was used in 4 patients with poor left ventricular function and poor collateral circulation, there were technical problems related to kinking of the left subclavian artery and discrepancy in size resulting in occlusion of the anastomosis in 2 patients. Reimplantation of the left coronary artery appears to be the most ideal surgical technique but it is not always possible because of insufficient length of the detached left coronary artery, depending on the location of the orifice on the pulmonary trunk. Because of this reason in one of our cases (case 8), reimplantation was not possible, therefore an interposition graft with autologous saphenous

vein was used. The most reasonable approach would be to excise the left coronary artery with a cuff of pulmonary trunk for reimplantation as the first step. If the length does not permit reimplantation, saphenous vein interposition could be performed, although there is still concern about the long term fate of the vein graft. Laborde, et al., recently reported superior results of the direct reimplantation of the coronary artery.¹²

In small infants, when the autogenous saphenous vein is of too small a size, a homograft implantation¹⁹ would be a reasonable option.

Surgical outcome in the presence of left ventricular dysfunction is not favorable. Two of the three patients who died in our series had poor left ventricular function (LVEDP= 20 mm Hg).

On the basis of recent advances in coronary artery surgery and myocardial protection, we suggest the following in the management of these patients:

1) All infants with evidence of myocardial ischemia on ECG should have myocardial scan and cardiac catheterization.

2) These patients should undergo surgical reimplantation of the left coronary artery. This is the ideal method but saphenous vein interposition can be used when reimplantation is not feasible.

3) All surgical anastomoses should be done on a non-beating, quiet heart using microsurgical technique.

4) Ligation of the left coronary artery is not recommended and should be abandoned.

5) Surgical treatment should not be delayed because once left ventricular function deteriorates, the prognosis is uniformly hopeless regardless of the surgical therapy.

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LOS OBJETIVOS DE SALUD PARA ESTADOS UNIDOS EN 1990 Y SU APLICACION A PUERTO RICO.

III. Enfermedades de Transmisión Sexual

Resumen: De las once metas nacionales de salud para 1990 referentes a las enfermedades de transmisión sexual, dos ya están aparentemente conseguidas en Puerto Rico, seis están bajo estudio y/o siendo perseguidas, y tres necesitan trabajarse desde el plano más básico. La obtención de estos objetivos en Puerto Rico, al igual que en otros estados, exige la cooperación de diversas instituciones gubernamentales, académicas y cívicas. También es de primera importancia la solución de problemas que han surgido después de la redacción de estas metas nacionales, como la transmisión de *Neisseria gonorrhoeae* productora de penicilinas, y el síndrome de inmunodeficiencia adquirida.

Abstract: Of the eleven national health goals for 1990 alluding to sexually transmitted diseases, two have been apparently achieved in Puerto Rico, six are under study and/or being pursued, and three need to be developed from the very basic stages. The achievement of these objectives in Puerto Rico, as in other states, requires the cooperation of many governmental, academic and voluntary institutions. Major efforts are also required to solve problems that were recognized after the establishment of the national objectives, namely, the transmission of penicillinase-producing *Neisseria gonorrhoeae* and acquired immunodeficiency syndrome (AIDS).

En 1990 el Servicio de Salud Pública de los Estados Unidos ("U.S. Public Health Service") publicó unas metas para el mejoramiento de la salud de los habitantes del país en los próximos diez años.¹ Quince asuntos prioritarios fueron identificados: control de la hipertensión, planificación familiar, embarazos y salud infantil, inmunizaciones, enfermedades de transmisión sexual (ETS), control de agentes tóxicos, seguridad y salud ocupacional, prevención de accidentes y control de traumatismos, fluorización y salud dental, vigilancia y control de enfermedades infecciosas, fumar y el deterioro en la salud, abuso de alcohol y drogas, nutrición, condicionamiento físico y ejercicio, control de la tensión y el comportamiento violento. Dentro de cada área se especificaron los objetivos a alcanzar para 1990. Estos

objetivos (226 en total), planteados de manera mensurable, se desarrollaron en consultoría con más de 500 expertos de los sectores público y privado, que representaban agencias de salud federales, estatales y locales, grupos de consumidores, organizaciones de voluntarios y profesionales de salud. Las metas se establecieron tomando en cuenta las tendencias actuales de factores pertinentes, tales como cambios demográficos, estilos de vida y la disponibilidad de fondos, y detallando lo que se asumió ocurriría con estos factores en la década de 1980 a 1990. Las metas han de alcanzarse por los esfuerzos de toda la gama de agencias e instituciones públicas y privadas, de personas y comunidades, y no se han establecido como una responsabilidad federal. El gobierno federal se ve llamado a dirigir, catalizar y respaldar un esfuerzo colectivo con móviles locales, y lleva a cabo evaluaciones periódicas del progreso hacia esos objetivos.^{2, 3} Este artículo presenta la situación actual en Puerto Rico respecto a los objetivos relacionados con las enfermedades de transmisión sexual.

Métodos

Las metas aquí reseñadas fueron traducidas por el autor y se citan, en comillas, tal como aparecen en el texto original en inglés.¹ Se ha conservado, como en el original, el término "vacuna" para significar inmunización activa, aunque ninguno de los objetivos esté relacionado con la vacunación contra viruela. Cada meta se rotuló "AA", "P", o "I" de acuerdo con los siguientes criterios: AA (aparentemente alcanzada) si la evidencia disponible indica que el estado de la enfermedad o de la técnica de salud pública al momento actual en Puerto Rico concuerda con lo deseado para 1990; P (perseguida) si hay al momento un esfuerzo de recogida de datos respecto al problema y/o un programa establecido para el control de la enfermedad o prestación del servicio; I (indocumentada) si la información específica que estipula el objetivo no se conoce para Puerto Rico. Los datos de población se obtuvieron de la División de Recursos Humanos, Área de Planificación Económica y Social, de la Junta de Planificación de Puerto Rico. Las cifras indican el tamaño estimado de la población de Puerto Rico al primero de julio de cada año estudiado (1973 a 1983). Los datos de morbilidad provienen del Programa de Control de Enfermedades de Transmisión

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Sexual (PCETS), dirigido por el doctor Yamil H. Kouri, en el Recinto de Ciencias Médicas de la Universidad de Puerto Rico. Las cifras de morbilidad están presentadas por año calendario. Las de sífilis congénita sólo están disponibles por año fiscal, y se han utilizado como si correspondieran al año calendario en que comienza el año fiscal. Las tasas de morbilidad (por 100,000 habitantes) están calculadas usando la población total de Puerto Rico, excepto para la sífilis congénita, donde se utilizó como denominador la población de edad menor de un año. Los datos de mortalidad se extrajeron de los análisis detallados inéditos que hace la Oficina de Estadísticas, Análisis y Control de Información (Administración de Facilidades y Servicios de Salud, Departamento de Salud) de los certificados de defunción que se cumplimentan cada año; los datos para 1982 y 1983 no estaban disponibles al momento de esta investigación. Hasta 1978 se usó la octava edición de la "International Classification of Diseases, Adapted for use in the United States" (ICDA-8), para identificar por números las causas de muerte, cambiando en 1979 a la nueva edición (ICDA-9).^{4, 5} Las rúbricas correspondientes a las enfermedades aquí estudiadas fueron las siguientes: sífilis-091-97; sífilis congénita-090; gonorrea-098. Las tasas por enfermedad en Estados Unidos se tomaron del "Annual Summary 1982: reported morbidity and mortality in the United States".⁶

Objetivos para 1990

Mejoramiento del estado de salud

a. "Para 1990 la incidencia informada de gonorrea debe reducirse a una tasa de 280 casos por 100,000 habitantes." - AA

La tasa actual reportada en Puerto Rico (tabla 1) está muy por debajo de la tasa declarada para los Estados Unidos y aún es 66% menor de la meta estipulada para 1990. Es razonable suponer que la tasa de incidencia real en la Isla es superior a la reportada, pues médicos y pacientes tienen renuencia a que se transmita la información personal sobre ETS. Sin embargo, hay que recalcar que los datos de incidencia que informa el PCETS no incluyen sólo las notificaciones de médicos y clínicas de ETS, sino que también abarcan un programa

Tabla 1

Gonorrea en Puerto Rico, 1973-83

Año	Muertes	Casos	Población total	Tasa de incidencia por 100,000 habitantes
1973	0	4,236	2,872,300	147
1974	1	3,034	2,890,000	105
1975	0	2,912	2,938,800	99
1976	0	2,703	3,018,300	90
1977	0	3,126	3,074,100	102
1978	1	2,168	3,121,600	70
1979	0	2,062	3,160,700	65
1980	0	2,796	3,206,900	87
1981	0	3,432	3,246,800	105
1982		2,645	3,263,273	81
1983		3,126	3,266,900	96

Tasa Estados Unidos 1982 418

Meta Puerto Rico 1990 280

de cernimiento para gonorrea. Este se lleva a cabo desde 1973 en las clínicas de planificación familiar, cuidado prenatal y ginecológico del Departamento de Salud en toda la isla, y revela una prevalencia muy estable, entre 2 y 3%, de cultivos positivos para *Neisseria gonorrhoeae* en una población que se encuentra entre las veinte mil y treinta mil mujeres examinadas cada año.

b. "Para 1990 la incidencia informada de enfermedad pélvica inflamatoria ("pelvic inflammatory disease - PID") gonocócica debe reducirse a una tasa de 60 casos por 100,000 mujeres en la población. (En 1978 la tasa estimada era 130 casos por 100,000 mujeres.)" - P

El problema de "PID" en la Isla no es tan severo como para ser fácilmente identificable. En los cuatro años de 1980 a 1983 las clínicas del PCETS en Santurce y Río Piedras han visto 46 casos de "PID" gonocócico y 311 de "PID" no gonocócico, en 21,962 mujeres, o sea 1.6 casos de "PID" por 100 pacientes mujeres. Estos números todavía no revelan la frecuencia del problema en la población general, pero señalan la relativa rareza de los casos en las clínicas. El PCETS ha diseñado protocolos para definir las características y la incidencia de la enfermedad en los grupos socioeconómicos y etarios de las mujeres de Puerto Rico.

c. "Para 1990 la incidencia informada de sífilis primaria y secundaria debe reducirse a una tasa de 7 casos por 100,000 habitantes por año, con una reducción en sífilis congénita a 1.5 casos por 100,000 niños menores de un año." - P

En contraste con la situación informada para gonorrea, la tasa de sífilis primaria y secundaria en Puerto Rico es considerablemente mayor que la tasa en los Estados Unidos (tabla 2). En ambos lugares hay una tasa mayor de gonorrea que de sífilis, aunque la diferencia en magnitudes es mucho más marcada en los Estados Unidos. El sistema de vigilancia de sífilis es mucho más sencillo que el de gonorrea porque una gran proporción de los diagnósticos de sífilis se basan en el resultado de exámenes serológicos, y los laboratorios están legalmente obligados a declarar los exámenes serológicos positivos. Estas pruebas además se exigen por ley, en personas sin síntomas, para certificados de matrimonio y de salud. El diagnóstico de gonorrea, sin embargo, se hace frecuentemente sin cultivos, mediante evaluación clínica o resultados de examen microscópico en oficinas privadas o salas de emergencia.

La incidencia de sífilis congénita informada en Puerto Rico (tabla 3) es muy similar a la informada en los Estados Unidos, pero todavía es 391% mayor de lo deseado para 1990. El PCETS está planeando una compañía de educación pública, con especial énfasis en las clínicas prenatales, para informar a las embarazadas sobre la sífilis congénita y su prevención. La meta del PCETS es que no haya ningún caso de sífilis congénita en Puerto Rico de 1985 en adelante.

d. "Para 1990 la incidencia de infección seria neonatal debida a agentes transmitidos sexualmente, especialmente herpes y clamidia, debe reducirse a una tasa de 8.5 casos de herpes diseminado neonatal por 100,000 niños

Tabla 2

Sífilis Primaria y Secundaria en Puerto Rico, 1973-83			
Año	Muertes	Casos	Tasa por 100,000 habitantes
1973	6	779	27
1974	0	921	32
1975	4	738	25
1976	3	632	21
1977	2	603	20
1978	3	535	17
1979	6	611	19
1980	7	704	22
1981	2	718	22
1982		766	23
1983		905	28
Tasa Estados Unidos 1982			15
Meta Puerto Rico 1990			7

Tabla 3

Sífilis Congénita en Puerto Rico, 1973-83				
Año	Muertes	Casos	Población <1 año	Tasa de incidencia por 100,000 habitantes
1973	1	7	62,705	11.16
1974	0	9	62,443	14.41
1975	1	9	62,435	14.41
1976	1	14	63,416	22.08
1977	0	3	63,417	4.73
1978	0	9	63,906	14.08
1979	0	4	65,359	6.12
1980	1	6	64,556	9.29
1981	2	6	66,370	9.04
1982		5	67,785	7.38
1983		5	67,952	7.36
(preliminar)				
Tasa Estados Unidos 1982				7.11
Meta Puerto Rico 1990				1.50

menores de un año, y una tasa de 360 casos de pulmonía por clamidia por 100,000 niños menores de un año. (En 1979 cerca de 16.8 casos de herpes diseminado neonatal por 100,000 niños menores de un año y como 720 casos de pulmonía por clamidia por 100,000 niños menores de un año se estimaron haber ocurrido.)" - P

Al momento no hay datos de referencia disponibles para Puerto Rico. Va a ser muy difícil estudiar los problemas causados por herpes mientras no haya un laboratorio virológico de referencia para los hospitales públicos y privados. El PCETS acaba de recibir fondos federales para un "*Chlamydia* demonstration project", encaminado a investigar los problemas causados por *Chlamydia* que mencionan este objetivo y el próximo.

e. "Para 1990 la incidencia de uretritis no gonocócica e infecciones por clamidia debe reducirse a una tasa de 770 casos por 100,000 habitantes. (En 1979 la tasa estimada fue de 1,140 casos por 100,000 habitantes.)" - P (Ver objetivo anterior.)

Reducción de factores de riesgo

f. "Para 1990 la proporción de hombres y mujeres sexualmente activos que se protejan por el uso apropiado

de condones debe aumentar al 25% de aquellos a alto riesgo de adquirir ETS. (En 1979 la proporción estimada era menor de 10%)." - I

En este tema no hay datos de referencia disponibles para Puerto Rico.

Mayor concientización pública y profesional

g. "Para 1990 cada estudiante de tercer y cuarto año de escuela superior debe recibir información correcta y oportuna sobre ETS. (Al momento 70% de los sistemas escolares proveen alguna información sobre ETS, pero la calidad y lo oportuno de la comunicación varían grandemente.)" - I

El currículo de las escuelas públicas de Puerto Rico incluye cursos electivos sobre salud, donde se mencionan las ETS. Sin embargo, no tenemos datos como los que pide este objetivo para saber los conocimientos sobre ETS que tienen los estudiantes de escuelas públicas o privadas en la isla.

h. "Para 1985 al menos 95% de los proveedores de atención a la salud que vean casos sospechosos de ETS deben ser capaces de diagnosticar y tratar todas las ETS reconocidas actualmente, incluyendo herpes genital (diagnóstico por cultivo, terapia - si la hay disponible, y educación al paciente), hepatitis B (diagnóstico en varones homosexuales, prevención mediante vacuna y educación al paciente), y uretritis no gonocócica (diagnóstico, terapia y educación al paciente). (No hay datos de referencia disponibles.)" - P

Un gran número de profesionales de la salud asistió al Primer Congreso Mundial de ETS, realizado en San Juan en 1981. Este año (1984-85) el PCETS comenzó un programa de estudios post-residencia ("fellowship") en ETS. El "fellowship", de tres años de duración, admitió este año un pediatra. Admitirá, de ahora en adelante, dos médicos cada año, provenientes de diferentes disciplinas (como pediatría, medicina interna, medicina de familia y ginecología), y está coordinado con otras divisiones del Recinto de Ciencias Médicas, como por ejemplo, bacteriología y enfermedades infecciosas. El PCETS lleva a cabo cursos periódicos para entrenar personal de salud en el diagnóstico y tratamiento de ETS. De 1980 a 1984 se han adiestrado 319 personas, mayormente médicos y profesionales de enfermería. Aunque se planea aumentar el número de cursos ofrecidos cada año, otras entidades además del PCETS tendrán que ofrecer entrenamientos para que los miles de profesionales que puedan ver casos de ETS estén debidamente enterados de los últimos conocimientos en el campo. En médicos nada más el número es mayor de tres mil, ya que para 1980 había en la isla 2,763 médicos de medicina general, médicos de familia, internistas, pediatras y obstetras ginecólogos.⁷

Mejoramiento en los servicios y la protección

i. "Para 1990 al menos 50% de las grandes industrias y agencias del gobierno que ofrezcan programas de cernimiento y promoción de salud en el lugar de empleo deben proveer servicios sobre ETS (educación y los exámenes apropiados) como parte de esos programas." - I

No hay datos de referencia disponibles para Estados Unidos ni para Puerto Rico.

Mejoramiento en los servicios de vigilancia y evaluación

j. "Para 1985 debe haber datos disponibles en detalle adecuado (pero en agregados estadísticos para mantener la confidencialidad) para determinar la existencia de uretritis no gonocócica, herpes genital y otras ETS en cada área local, y para recomendar estrategias para prevenir ETS y sus complicaciones." - AA

La ley 81 del 4 de junio de 1983 ("Para establecer todo lo relacionado con la prevención y tratamiento de las ETS en Puerto Rico") y el reglamento número 51 del Secretario de Salud, del 23 de agosto de 1983, para la implementación de la misma ley, consideran como ETS y de declaración obligatoria por los médicos, las siguientes condiciones: sífilis, gonorrea, Herpes simplex genital, hepatitis B, chancroide, granuloma inguinal, linfogranuloma venéreo, verrugas genitales ("condyloma acuminata"), síndrome de inmunodeficiencia adquirida "(AIDS)", uretritis no específica, uretritis no gonocócica, tricomoniasis vaginal, moniliasis vaginal (candidiasis), ladillas ("pediculosis pubis"), escabiosis (sarna humana), y cualquier otra enfermedad que en el futuro, previa la investigación científica pertinente, se determine por el Secretario de Salud como una enfermedad de ETS. El PCETS lleva las estadísticas a nivel de municipalidad, y en San Juan, por sectores de la ciudad (San Juan/Río Piedras).

k. "Para 1990 los sistemas de vigilancia epidemiológica deben haber mejorado lo suficiente como para que al menos 25% de las ETS diagnosticadas en facilidades médicas sea notificado, y que definiciones uniformes se usen en todo Estados Unidos. (No hay datos de referencia disponibles.)" - P

Como se ha comentado anteriormente, el sistema de vigilancia epidemiológica de las ETS varía en eficiencia de acuerdo a los medios de diagnóstico (clínico o por pruebas de laboratorio) y a las fuentes de información (médicos privados o laboratorios). Aunque es difícil creer que actualmente menos del 25% de las ETS se esté informando, no hay datos para asegurar qué proporción de las que ocurren se notifica al Departamento de Salud. La nueva ley que regula la notificación de ETS (ley 81 de 1983) ayudará, sin duda, a mejorar el sistema de vigilancia.

Discusión

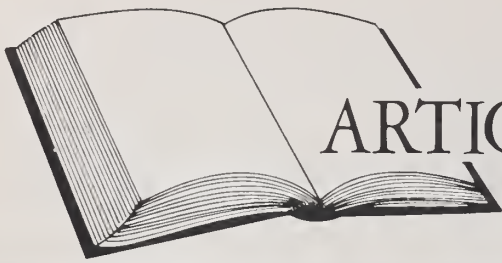
De los once objetivos para 1990 descritos en este artículo, dos han sido aparentemente alcanzados. El objetivo J, que se refiere a la vigilancia epidemiológica y la preparación de estadísticas de morbilidad, está firmemente establecido en los procedimientos del PCETS. El objetivo A, referente a la incidencia de gonorrea, necesita de verificación mediante un estudio de la sensibilidad del sistema de notificación de casos. Seis de los once objetivos están comenzando a estudiarse o están siendo perseguidos hace tiempo. Uno de ellos (objetivo K) exige la medición de la sensibilidad del sistema de vigilancia epidemiológica de las ETS. No es sorprendente que muchos de los objetivos sin conseguir estén relacionados a los diagnósticos de laboratorio más difíciles o más recientemente popularizados (objetivos D, E), y a las respuestas de la sociedad para educar sus ciudadanos

sobre sexualidad y ETS (objetivos F, G, H, I).

Los primeros dos artículos de esta serie examinaron los objetivos relacionados con la vigilancia y control de las enfermedades infecciosas, y las enfermedades prevenibles por vacunación.^{8, 9} A diferencia de los programas discutidos en esos artículos, los programas de control de ETS, en toda la nación, han sufrido embates poderosos que han cambiado el horizonte de sus problemas de forma que no podían prever los redactores de las metas para 1990. La aparición de *Neisseria gonorrhoea* productora de penicilinasa ("penicillinase-producing *N. gonorrhoeae* - PPNG") y el "AIDS" han forzosamente desarticulado los planes de distribución de recursos para el control de ETS a largo plazo.¹⁰ Ambos problemas han tenido un fuerte impacto en Puerto Rico. Las "PPNG" fueron detectadas por primera vez en la isla en 1982. Un esfuerzo especial de búsqueda y tratamiento de casos y contactos consiguió mantener la frecuencia de "PPNG" al 1.7% de los casos de gonorrea vistos en 1982, y al 1.0% de los casos en 1983. No obstante, la frecuencia de "PPNG" en los primeros seis meses de 1984 aumentó al 7.2% de los casos de gonorrea. Las primeras estadísticas de "AIDS" en Puerto Rico han sido ya reseñadas en las páginas del Boletín.¹¹ Desde entonces el número de casos ha seguido aumentando; en 1983 se notificaron 22 casos, pero en los primeros seis meses de 1984 se informaron 49 casos nuevos. Ambas enfermedades han presentado al PCETS nuevas exigencias en términos de pruebas diagnósticas costosas y tratamientos complicados y caros. No hay duda de que para proteger la salud pública, la solución de estos problemas es de gran importancia, aunque no estén entre los objetivos publicados para 1990.

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ARTICULOS DE REPASO

Coma: Pathophysiology and Procedure Guide

Manuel F. Casanova, M.D.

Abstract: Coma is a state of unarousable unresponsiveness. The patient is mute, unable to make purposeful movements, and lies with his eyes closed. Yet, there are several other similar states from which coma must be distinguished (e.g., locked-in syndrome, chronic vegetative state, brain death, etc.). Once a diagnosis of coma has been ascertained, proper actions must be taken to prevent death or any major neurological sequelae.

Resumen: Coma es un estado de conciencia en el cual la persona no responde a ningún tipo de estímulo. El paciente yace mudo, inmóvil y con los ojos cerrados. Sin embargo, hay otros estados similares de los cuales debe ser diferenciado (por ejemplo; el síndrome "locked-in", estado vegetativo crónico, muerte cerebral, etc.). Una vez el diagnóstico de coma se ha hecho con certeza, se deberán tomar las acciones apropiadas para prevenir la muerte u otras complicaciones neurológicas.

Coma is a state of unconsciousness from which a person cannot be aroused even upon painful stimulus. The patient lies mute with his eyes closed, is immobile, and is unable to yield the ordinary rudiments of a neurological examination. It is here that the Oslerian dictum, "listen to the patient, and he will tell you what is wrong with him", cannot possibly apply. A comatose person rapidly deteriorates and dies unless the proper diagnostic and therapeutic measures are executed.

The present report, directed to the busy clinician who requires a general knowledge of the field, includes a discussion on the pathophysiology of coma and a procedure guide which directs the clinician in a step-by-step fashion on how to approach a comatose patient.

States of Consciousness

The term "coma" is derived from the Greek work "koma", meaning deep sleep. However, regardless of any similarities attributed in the popular literature, sleep and coma must be considered quite separate entities.

Physiological studies have shown a decreased cerebral oxygen uptake during coma,^{1, 2} a finding quite unbecoming of sleep. Sleep is characterized as a recurrent event with certain electroencephalographic (EEG) stagings from which no neurological sequelae ensue. On the contrary, coma usually is a single event in the life of an individual and lasts less than four weeks. Coma bears a grave prognosis despite its cause. As such, coma is a symptom, not a disease process *per se*. Coma involves brain failure in the same sense that uremia implies renal failure.

A state of unconsciousness which lasts more than four weeks entitles a revision of the diagnosis of coma.² No matter how severe the brain damage might have been, comatose patients begin to make some "recovery" by two to four weeks after the initial insult. Although still mute, eyes may open and perform roving movements. Slow dystonic postural and reflex movements are made. Curiously enough, the EEG may show evidence of high voltage slow waves or some alpha rhythm of "wakefulness", even though the patient may never give any proof of higher mental (cortical) activity. This is a state in which only the vegetative functions of the individual persists without any hope for recovery.³ Its differentiation from brain death has more of a medicolegal importance than moral significance to the involved physician.

Coma must also be distinguished from such states as akinetic mutism and the "locked-in" syndrome. The former is a condition of prolonged survival in a relatively immobile and silent state. Occasional complex motor activity and speech may occur but not in response to the examiner's actions. The patient appears awake and can track different persons around the room, giving false hopes to the involved family for an eventual recovery. Bilateral basomedial frontal or rostral brainstem lesions have produced this syndrome.⁴

Utmost importance should be given to the recognition of any "locked-in" patient. These unfortunate individuals, although quadriplegic, are conscious; they hear and perceive somatic sensations. Motor activity is confined to lid and vertical eye movements, and these patients may communicate through Morse code. A

pontine lesion interrupting the corticobulbar and corticospinal tracts is usually implicated.

Although frequently used in the literature to imply distinct states of consciousness, such terms as "coma vigil" or the "apallic syndrome" should be abrogated. Coma vigil is actually a subtype of akinetic mutism resulting from frontal lobe damage and often includes areas of thalamus and hypothalamus. The apallic syndrome does not refer to a particular behavioral state but rather to an end result of diffuse degeneration of the cerebral cortex, as occurs with anoxic injuries. For further information, the interested reader is referred to the excellent work of Plum and Posner.²

Pathophysiology of Consciousness

Coma is the absence of consciousness. However, to take this as a definition would be inconclusive if we did not explain the meaning of the word "consciousness". This is a difficult undertaking that has already been attempted by many scientists and philosophers. For our own purposes, to be conscious is to have an awareness of both our own existence and the immediate surrounding and to be able to interact accordingly. This implies an alert individual with a mental content which enables him to take heed of his sensations. Mental content or cognition is a function of the cortical apparatus and includes judgment, memory, intellect, orientation, and the ability to use language. As such, it represents one of our highest and most intricate capabilities.

A state of alertness is provided by the reticular activating substance in the brainstem. This subcortical system is responsible for the arousal of the individual. Its existence and proper functioning is a prerequisite to the neurological testing of mental content, i.e., a patient must be alert in order to properly test for memory, judgment, orientation, intellect, and language. Thus, consciousness is a phenomenon which transcends the individual cells of an organism and depends on a myriad of interactions involving multiple levels of the brain working at a proper time constant. Of these, both the reticular activating system and the cerebral cortex play vital roles.⁵ It should be easily deduced that coma may be the result of three different pathological processes: those affecting, in a diffuse and bilateral manner, the cerebral cortex; those affecting the ascending reticular activating formation of the upper brainstem and thalamus; and those which cause coma by depressing both the cerebral cortex and reticular activating system (e.g., metabolic disorders).

Diagnostic and Therapeutic Procedures in Coma

Coma is a medical emergency which requires prompt and organized treatment in order to prevent death or any major neurological sequela. The following guide is provided to facilitate such a plan of action and to give the physician in charge the fundamentals which may lead to a proper diagnosis.

Priorities

1. Establish an adequate airway, i.e., be aware of the need for artificial respiration or the insertion of a cuffed endotracheal tube. Airway obstruction is prone to occur

in coma due to hypotonia of the tongue and pooling of secretions. Relaxation of the tongue may cause it to fall backwards against the posterior pharyngeal wall and occlude the airway. Until proven otherwise, noisy breathing means obstructed breathing.

2. Maintain blood pressure.
3. Withdraw blood for laboratory analysis.
4. Guarantee cerebral metabolic needs.
 - a. 50 ml 50% dextrose i.v. when judged necessary
 - b. 200 mg thiamine i.v. with Wernicke's encephalopathy.

(Thiamine should precede glucose in alcoholic patients.)

5. Position the patient properly to avoid aspiration and decubitus ulcers, i.e., semiprone with the head down and frequent side to-side turning. This posture is contraindicated when a mass lesion is suspected. Aspiration pneumonitis should also be avoided by prevention of vomiting (gastric tube) and removing stagnant secretions as soon as they accumulate.

Other considerations, when appropriate, include the following:

1. Decrease elevated intracranial pressure (ICP). Hyperventilation is the fastest way to reduce ICP. However, a severe drop in PaCO_2 may compromise cerebral blood flow. If hyperventilation is used, PaCO_2 should be maintained at 25-30 torr (further lowering may be detrimental). Osmotic agents constitute the classical therapy to decrease ICP; however, congestive heart failure may be precipitated in susceptible patients. Dialysis is necessary in patients with renal failure to remove osmotic agents and excess free water. Diuretics can be employed in patients who cannot tolerate the increased circulatory volume which occurs with osmotic agents.

2. Anticonvulsants.

3. Treatment of infections — those that begin before or shortly after hospitalization are usually the result of aspiration.

4. Restore acid-base balance.

5. Control body temperature. Hyperthermia increases cerebral metabolic needs. High fever should be lowered by using ice packs. A high temperature may indicate an atropine-type derivative or hallucinogen ingestion. Hypothermia may be a sign of Wernicke's encephalopathy, hypoglycemia, myxedema coma, pituitary myxedema coma, prolonged exposure, depressant drug poisoning, or brainstem infarct.

6. Consider naloxone (Narcan). In cases of narcotic overdose, 0.4 mg naloxone should be given i.v. every five minutes until the patient recovers consciousness.

7. Give proper attention to bladder and bowel functions. A retention catheter is sometimes necessary and should be clamped intermittently to maintain bladder tone.

8. Beware of major complications, such as neurogenic pulmonary edema and disseminated intravascular coagulation, both of which tend to occur with traumatic comas.

9. Control agitation.

10. Protect the eyes.

On physical examination, emphasize the following:

1. State of consciousness.
2. Pattern of breathing (Fig. 1) and pulse rate.

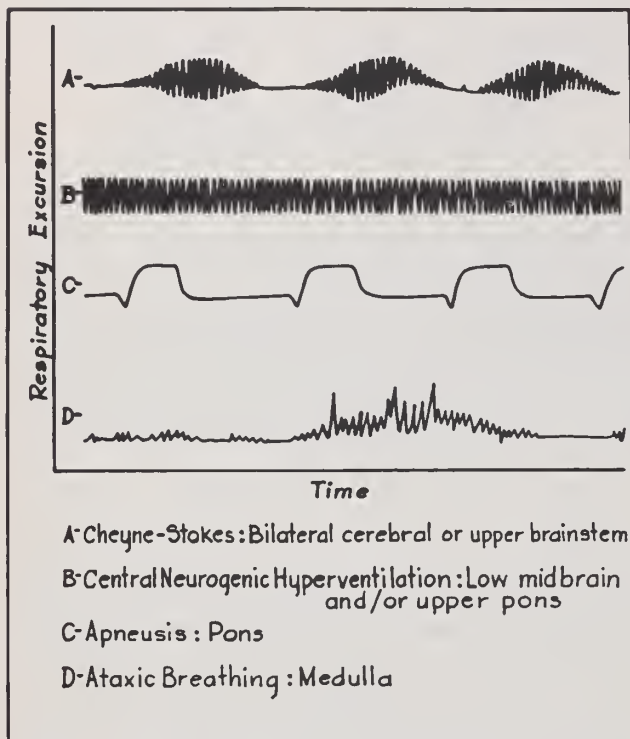


Figure 1. Breathing patterns of patients in coma.

a. Pattern of breathing

1) Cheyne-Stokes indicates hemispheric dysfunctions with an intact brainstem; it may be seen in transtentorial herniation, bilateral cerebral vascular occlusive disease, metabolic disorders, and congestive heart failure.

2) Central neurogenic hyperventilation (rapid deep breathing) implies damage to the brainstem tegmentum. It may be seen with lesions to the aforementioned area, hypoglycemia, anoxia, or compression due to a supratentorial mass.

3) Ataxic (irregular) or gasping breathing is a terminal event, the consequence of medullary dysfunction.

b. Pulse rate

1) If slow, it should suggest heart block or, if combined with hypertension, an increased intracranial pressure.

2) If rapid, the possibility of an ectopic cardiac rhythm with insufficiency of cerebral circulation should be considered.

3. The patient's odor may offer a diagnostic clue to alcohol intoxication, diabetic coma, uremia, or hepatic failure.

4. In the head, neck, and extremities, nuchal rigidity with resistance to passive flexion (but not to extension or rotation) is suggestive of meningitis or subarachnoid hemorrhage. Examine the patient for any evidence of head trauma, blood or cerebrospinal fluid in cranial orifices. Battle's sign (subcutaneous blood over mastoid

area) may indicate basilar skull fracture. Palpation may reveal pathological depressions. Look for needle marks on extremities.

5. Size and reactivity of the pupils (Fig. 2).

a. Reactive pupils, by either light or accommodation, imply an intact midbrain; their presence in conjunction with the absence of other neurological signs is characteristic of metabolic or toxic coma. Structural lesions producing coma tend to fix the pupils.

b. Pontine damage produces pinpoint pupils and respiratory abnormalities, a situation somewhat similar to a narcotic overdose. A lesion in the lower pons may give rise to ocular bobbing (brisk downward movement of both eyes with a slow return to the original position).

c. A dilated pupil suggests a lesion at the junction of the carotid and the posterior communicating arteries (e.g., aneurysm) or in the midbrain, as with uncal herniation.

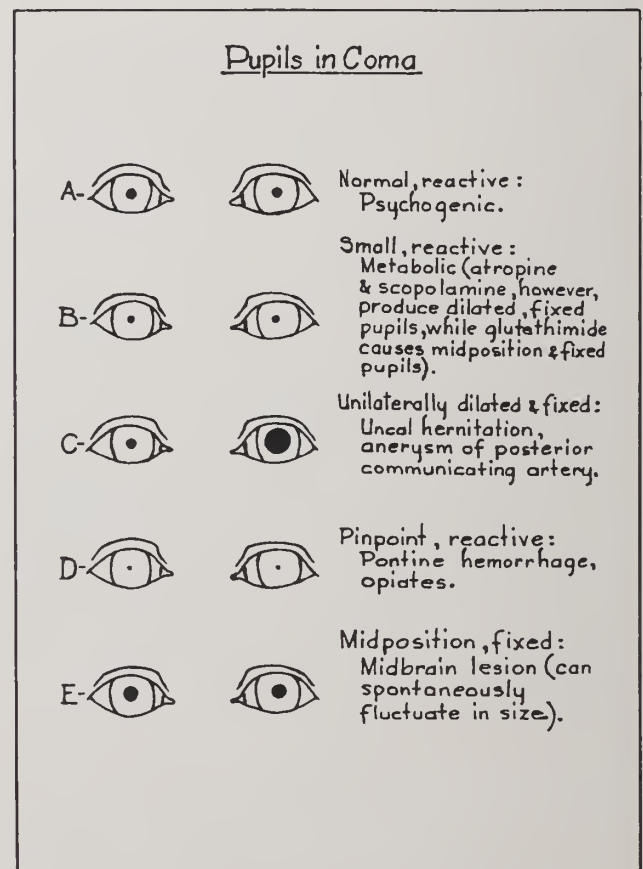


Figure 2. Pupillary size and their reaction to light of patients in coma.

6. Eye movements during oculoccephalic (doll's eyes) maneuvers and oculovestibular responses: Absent or abnormal eye movements indicates brainstem disease. Thalamic hemorrhages may exhibit a downward deviation of the eyes. If only one eye abducts and the other fails to abduct, there is probably an interruption of the medial longitudinal fasciculus. With large cerebral lesions, the eyes may be held conjugately to one side (looking at the lesion) and away from the paralysis. Eyes look toward the

side of the paralysis with unilateral pontine lesions (looking away from the lesion).

In the presence of coma, a full range of extraocular movements rules out an infratentorial structural lesion as the cause of coma. Absence of extraocular movements in the presence of normal-sized reactive pupils indicates that the cause of coma is metabolic.

7. In skeletal muscle motor responses during stimulation, observe any decorticate or decerebrate posturing; both of these findings may appear with either structural or metabolic diseases. When the lower pons is involved in the disease process, flaccid quadriplegia replaces decerebrate posturing. Muscular twitches are often seen in metabolic comas. Reflex withdrawal implies involvement of the corticospinal tract.

Initial studies include arterial blood gases, complete blood count with differential, serum electrolytes including magnesium (do anion gap), T4 in cases of suspected myxedema coma, chest x-rays, liver function studies, and electrocardiogram.

Other Studies

Neurodiagnostic

Skull X-rays

Unconscious patients with evidence of trauma should be treated as if cervical spine fracture had occurred until appropriate x-ray studies are obtained. Skull x-rays should be evaluated for displacement of the calcified pineal gland, fractures, abnormal calcifications, and metastatic deposits. An enlargement of the sella turcica in the presence of shock, fever, and a slightly bloody cerebral spinal fluid means pituitary apoplexy and immediate therapy with intravenous steroids is required.

Electroencephalogram (EEG)

An EEG indicates whether the process causing coma is diffuse or focal; it is useful as an adjunct in the diagnosis of brain death.

Brain Scan

The brain scan is a screening tool for subdural hematomas, vascular malformations, and neoplastic diseases.

Computerized Tomography Scan

The computerized tomography scan is a noninvasive technique considered the diagnostic procedure of choice when a focal mass lesion is suspected in a comatose patient. It differentiates supratentorial from infratentorial lesions, identifies the nature of the pathological process, and guides any further therapeutic endeavor.

Lumbar Puncture

Bloody cerebrospinal fluid occurs in cerebral contusion, subarachnoid hemorrhage, brain hemorrhage, anthrax meningitis, and occasional hemorrhagic infarcts. If the pressure is elevated greatly, hypertonic solutions should be given intravenously.

Brainstem Auditory-Evoked Potentials

Brainstem auditory evoked potentials are relatively resistant to metabolic insults. Their normal presence with a flat EEG implies a central nervous system depressant drug overdose and the potential reversibility of the comatose state. Contrary, the absence of waves 3 and 4/5 in the presence of wave 1, even when the EEG is normal, suggests brainstem damage. Absence of brainstem auditory evoked potentials entitles a cautious interpretation, since prior otological disturbances may be responsible, and a proper history is usually impossible to obtain in a comatose patient.

Other studies include toxic screening (blood is the ideal material; however, certain drugs, such as phenothiazides and amphetamines, are best detected in the urine), vomitus or gastric analysis, and stool examination.

Conclusion

Coma is a state of unresponsiveness from which a person cannot be aroused. It is a medical emergency which requires prompt treatment. Safeguarding the vital signs is the first step of any effective therapeutic endeavor. After stabilizing the patient, the clinician should perform a well-organized physical examination directed at localizing any underlying lesion and clarifying its nature. Supratentorial lesions cause neurological dysfunction at one level which progress in a rostral-caudal fashion. Focal signs occur early, and coma supervenes late. Infratentorial lesions usually cause discrete localization within the brainstem, abnormal oculovestibular or oculocephalic testing, and bizarre respiratory patterns. Coma is seen early with infratentorial lesions. Partial dysfunction occurring simultaneously at many levels is suggestive of a metabolic derangement. Patients with psychiatric unresponsiveness (e.g., hysteria or catatonia) have a normal EEG, caloric-induced nystagmus is intact, and there are no abnormal motor findings. Supratentorial or infratentorial focalization is usually the result of a structural lesion which may require further diagnostic procedures such as a computerized tomography scan. Consultation of a neurologist or neurosurgeon is recommended in these cases. Generalized disturbances causing coma are usually the result of metabolic derangements, hypoxia, or intoxication. Diagnostic workup in these patients may require, among other things, an EEG, electrocardiogram, arterial blood gases, toxicology studies, and blood chemistry studies such as SMA-18. The expert advice of either a neurologist or internist is recommended.

Acknowledgement

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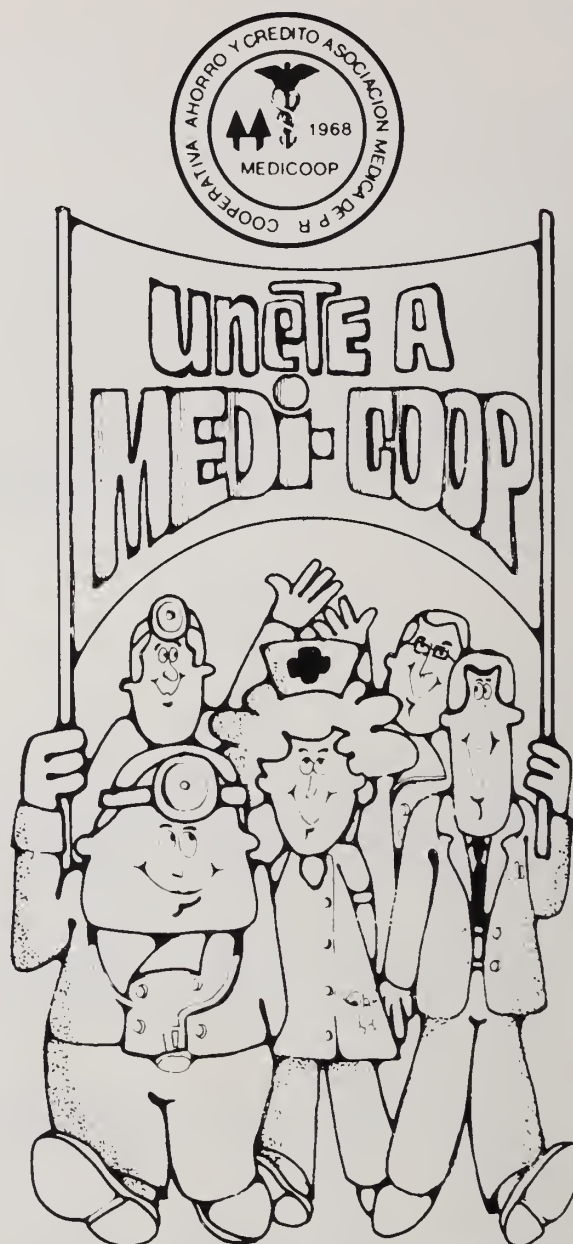
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Pregnancy In Patients With Tricuspid Atresia

Charles D. Johnson, M.D., FACC

Summary: A 64 1/2-year-old woman with Type Ib tricuspid atresia, the oldest known patient with such, who sustained an incomplete abortion at age 40 1/2 years, is reported. Autopsy also revealed an abnormal mitral valve and an extremely rare left atrial to right ventricular communication. Pregnancy in tricuspid atresia is reviewed, emphasizing the dismal maternal and fetal prognosis.

Cyanotic congenital heart disease occurs in one of every 14,000 to 15,000 pregnancies. Tricuspid atresia (TA) comprises 1-3% of congenital heart disease. Pregnancy has been documented some 24 times in 14 or more patients with TA. It is hazardous and marked by congestive heart failure (CHF), worsening of the patient's status, abortions, impaired fetal growth, prematurity and high maternal and perinatal mortality and morbidity. This is supported by two maternal deaths (14% mortality), only 8 survivors (33%), at least temporary, and an abortion rate of 54%; the latter is especially high with polycythemia. The prognosis may be improved by shunt surgery evidenced by operated TA patients bearing babies, but complications yet occur.¹⁻⁴

Case Report

Medical details of this 64 1/2-year-old female are reported elsewhere.⁵ In summary, her life was characterized by physical limitation, marked cyanosis, clubbing and hypoxemia, polycythemia, bleeding, CHF, cardiomegaly, a loud pansystolic murmur and mitral regurgitation. Atrial flutter-fibrillation and a cerebrovascular accident complicated her last years. Autopsy revealed Type Ib TA, and an extremely rare left atrial to right ventricular communication. Genitalia, uterus and both ovaries were normal at autopsy.

Her menarche occurred at age 16 years. She married at age 35. Menses ceased at age 36, and vaginal bleeding ensued at age 38 years. An incomplete abortion was diagnosed in 1958, at the age of 40 1/2 years. Unfortunately, no further obstetrical history is available.

Discussion

This 64 1/2-year-old woman, the oldest known case with TA,⁵ suffered an incomplete abortion at 40 1/2 years of age. Table 1 characterizes at least 14 cases of TA known to have been pregnant (information was sometimes incomplete).¹⁻¹¹ A minimum of 5 had undergone previous shunt surgery.

TABLE 1

Pregnancy in Patients with Tricuspid Atresia				
Author Year Reference	Age When Pregnant	Type	Results	Comments
Cooke ⁶ , 1959	41	I B	Dyspnea and cyanosis. Delivered premature baby. Patient survived.	
Present Case ⁵ , 1983	40 1/2	I B	Incomplete abortion. Patient survived until age 64 1/2 years. Left atrial to right ventricular communication. Mitral regurgitation.	
Jordan ¹ , 1966	37	I C	Pregnancy terminated by cesarean section because of severe congestive heart failure. Patient survived.	
Hatjis ⁴ , 1983	30	I B	Glenn procedure at age 13 years. VSD with left to right shunt. Cyanosis, clubbing, cardiomegaly, systolic murmur, S ₁ Hct. 45-60%, pO ₂ 38 mm Hg, normal ECG. Gestational age 32-33 weeks. Therapy-oxygen, phlebotomies, heparin and antibiotic prophylaxis, cesarean section. 10% abruptio placentae. Infant 960 g with fetal growth retardation and subsequent normal development. Mother had uneventful course.	
Novy ¹ , 1968	23	II C	Rheumatic fever. Dyspnea, hemoptysis, cyanosis, hypertension, polycythemia, oxygen saturation 72-79%, oxygen curve to right. ASD, large VSD, partial TGA, left ventricular enlargement, pulmonary hypertension. Spontaneous labor, delivered 1100 g infant with a Hb of 18 g who died at 40 hours of age with severe intrapulmonary hemorrhage. Second pregnancy-spontaneous abortion at 12 weeks. Class III. Mother later died suddenly after syncope.	
Fontan ⁸ , 1971	23	I B	Dextrocardia. Cyanosis. Cardiac failure during pregnancy. Premature birth. Patient died late postoperatively.	
Collins ¹ , 1977	23	I B	ASD. VSD. Bidirectional shunt. Blalock-Taussig shunt at age 8 years. 1968-pregnant and delivered a 2 lb infant who survived and developed. 1969- aborted at 2 months. 1970- Stroke. Spontaneous abortion at 2 months. Loud apical systolic murmur, diastolic murmur. Cyanosis since birth, clubbing, chest pain, pO ₂ 53-69 mm Hg, saturation 87-94%, First degree AV block, heart failure, emboli, seizures. Premature infant succumbed at 3 days of age	
Burwell & Metcalfe ² , 1958	21		ASD. Survived 3 spontaneous abortions. (note Novy ¹).	
Dubourg ¹⁰ , 1959	21	I B	Patient died at delivery "Morte de syncope".	
Taussig ³ , 1959 (Burwell)			ASD. Died in late pregnancy of massive hemoptysis.	
Reid ¹¹ , 1963			Boston. One case of tricuspid atresia.	
Taussig ² , 1973			After Blalock-Taussig shunts. a) one woman, operated at age 5 years, has had 2 children and 3 miscarriages. b) another woman had 2 miscarriages. c) another woman had one miscarriage.	

ASD= atrial septal defect, AV= atrioventricular, Hb= hemoglobin, Hct=hematocrit, TGA= transposition of the great arteries, VSD= ventricular septal defect.

Novy, Collins and associates^{1, 3} noted that fetal outcome in TA patients was so dismal and maternal mortality so great, that therapeutic abortion and sterilization were recommended. Should pregnancy occur, anticoagulants should be started immediately. At delivery, hypotension from conduction blocks or hemorrhage must be avoided since "shunt reversal could lead to intractable heart failure."

Hatjis et al⁴ recently described a patient with TA and marked hypoxemia who gave birth (cesarean section) without complications. The authors emphasized the importance of intensive maternal-fetal monitoring of multiple biochemical and biophysical parameters (hematological profiles, blood gases, P₅₀, estriol, progesterone, lecithin-sphingomyelin), and management with bed rest, portable oxygen, phlebotomies, prophylactic heparin and antibiotics, and cesarean section.

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Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under "Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "Causal Relationship Unknown" if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C.*
Amalia Martínez Picó, M.D., F.A.C.C.*
Margarita Martínez-Cruzado, M.D.**

Un joven de 15 años es referido a nuestro servicio para estudios diagnósticos invasivos. Tiene un soplo cardíaco desde la infancia sin evidencia de insuficiencia cardíaca, cianosis, dolor precordial, intolerancia al ejercicio ni síncope. Al examen físico se aprecia un adolescente bien nutrido con pulso, respiración y presión arterial normales. A la palpación del tórax hay accesibilidad ventricular izquierda, el punto de mayor impulso cardíaco está en el 6° espacio intercostal izquierdo a lo largo de la línea media-clavicular y hay frémito tanto en el 2° espacio intercostal derecho como en la hendidura supra-esternal. Se ausculta un soplo sistólico-eyectivo, rudo, grado IV/6 con acentuación mesosistólica, que se oye mejor en el segundo espacio intercostal derecho cerca del reborde esternal. El soplo se irradia a lo largo del borde esternal izquierdo superior y lado derecho del cuello y la espalda. No hay componente diastólico ni sonido de eyección. El S₁, S₂, y P₂ son normales y no hay S₃ ni galope. Los pulsos periféricos son normales en todas las extremidades. La Hb es de 14 gm, el electrocardiograma demuestra hipertrofia ventricular izquierda y en la radiografía de tórax se aprecia silueta cardíaca y vascularidad pulmonar normales.

El aortograma retrógrado que se ilustra a continuación permitió identificar el defecto cardíaco congénito del niño.

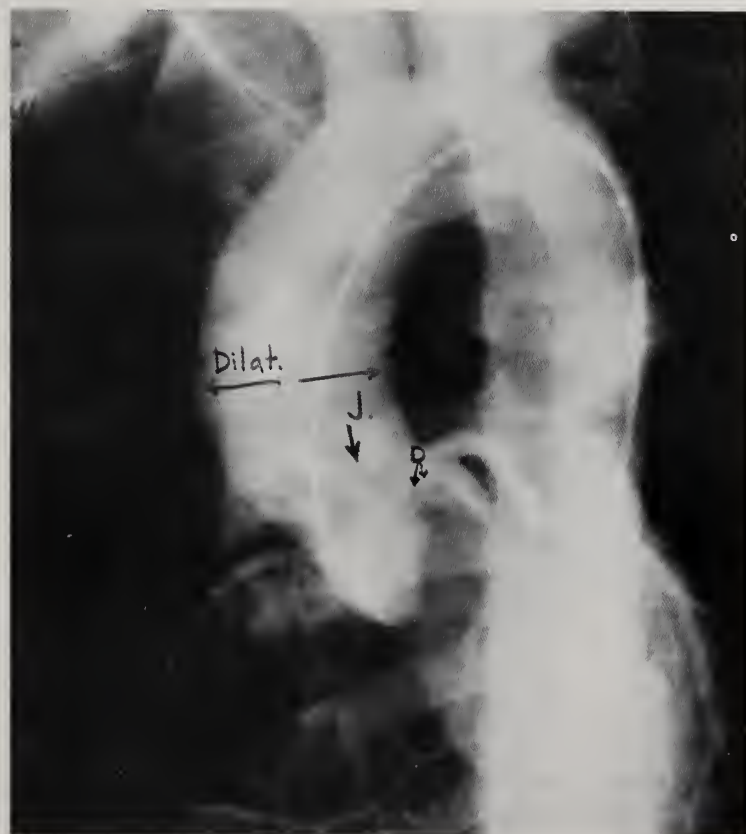


Figura 1. Aortograma retrógrado, posición oblicua anterior izquierda, 60°

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¿CUAL ES SU DIAGNOSTICO?

Diagnóstico: Estenosis valvular aórtica

La estenosis valvular aórtica (AS) constituye aproximadamente el 6% de las cardiopatías congénitas. Algunos consideran la válvula aórtica bicúspide el defecto cardíaco congénito más frecuente¹ y la causa más común de estenosis valvular aórtica congénita.

La estenosis aórtica es 4 veces más común en el hombre que en la mujer y en 20% de las veces se acompaña de otra cardiopatía congénita,² siendo las más frecuentes el ducto arterioso patente y la coartación de la aorta.

Los hallazgos clínicos en la estenosis aórtica pueden ser variados, dependiendo mayormente de la severidad de la estenosis y el grado de obstrucción que ella pueda causar. La mayoría de los niños con AS están asintomáticos, tienen un crecimiento y desarrollo normal y el soplo de AS es en muchos de ellos un hallazgo casual. El soplo sistólico característico de la AS es fuerte, de tonalidad áspera, configuración romboidea y suele escucharse mejor en la base, aunque en el recién nacido se ausculta mejor en el 3er. y 4to. espacio intercostal izquierdo. Esto es causado por la hipertrofia de ventrículo derecho que es normal para esa edad. El soplo, al igual que el frémito que puede acompañarlo, se irradia a la región supraesternal, cuello y apex. La configuración de este soplo es de utilidad en la valoración del grado de estenosis pues cuando el gradiente a través de la válvula estenótica es mayor de 75 mm Hg, el soplo tiende a alcanzar su "pico" en las últimas 2/3 partes de la sístole.³ En cerca de 25% de los niños con AS hay un soplo diastólico de insuficiencia aórtica. Este suele ser de poca intensidad, comienza justo después del segundo sonido y es de carácter decreciente. Puede estar presente también un sonido de eyección aórtico en el apex el cual es debido a la apertura de las valvas aórticas por lo que su presencia implica estenosis valvular aórtica leve o moderada. Pueden también estar presente en las AS un S₃ (sonido por vaciado diastólico temprano) y un S₄. Este último implica una obstrucción severa al tracto de salida ventricular izquierdo.⁴

Cuando el grado de AS es significativo, se puede palpar la actividad ventricular izquierda en el precordio. Se dice que si el gradiente sistólico a través de la válvula excede 25 mm puede palparse el frémito en la base con propagación por los vasos del cuello, carótida y subclavias. Los hallazgos clínicos juntos con el electrocardiograma, la radiografía de tórax y sobre todo el ecocardiograma permiten el diagnóstico clínico temprano de esta cardiopatía una vez se sospeche la misma. En muchos casos la ecocardiografía nos permite calcular los gradientes con facilidad y es de gran ayuda para un seguimiento de tipo no invasivo satisfactorio. Cuando la presencia de una obstrucción hemodinámicamente significativa a la salida ventricular izquierda se establece por los medio no invasivos disponibles debe hacerse un cateterismo cardíaco y un angiocardiograma. El cateterismo está indicado en todos aquellos pacientes con el diagnóstico clínico de AS en los cuales las pruebas diagnósticas no invasivas sugieran la posibilidad de una obstrucción ventricular izquierda moderada o severa. En todo paciente con AS y síntomas como disnea al esfuerzo, fati-

gabilidad, dolor anginoso o síncope que pueda relacionarse con la AS debe hacerse un cateterismo cardíaco.⁵ Con el cateterismo izquierdo por vía retrógrada pueden medirse gradientes (si alguno) así como precisar el lugar exacto de la obstrucción y la severidad de la misma. El ventriculograma izquierdo permite evaluar el tamaño de la cavidad ventricular izquierda, el grosor de su pared, la deformidad y movilidad valvular, el estado funcional de la válvula mitral y las arterias coronarias.

En el caso que presentamos el grado de estenosis valvular aórtica era tal que no permitió el paso del cateter a través de ella. Por ello se hizo un aortograma retrógrado (fig. 1) en el cual puede apreciarse la deformidad en "cúpula" de la válvula aórtica durante la sístole (D), el chorro o "jet" (J) central de sangre sin material de contraste proveniente del ventrículo izquierdo pasando a través de la válvula aórtica y la dilatación postestenótica de la arteria pulmonar principal (Dilat). La válvula aórtica estenótica durante la sístole ventricular característicamente adquiere forma de "cúpula" donde las valvas abren poco y encorvadas en sus bordes libres (fig. 2-a). En la válvula aórtica normal las valvas abren por completo de manera que en sístole estas quedan paralelas a la pared de la aorta ascendente (fig. 2-b). Cuando la válvula aórtica es normal, pero existe una estenosis subvalvular las valvas abren de forma incompleta. No abren paralelas a la pared aórtica pero permanecen rectas, sin encorvarse, (fig. 3-c)

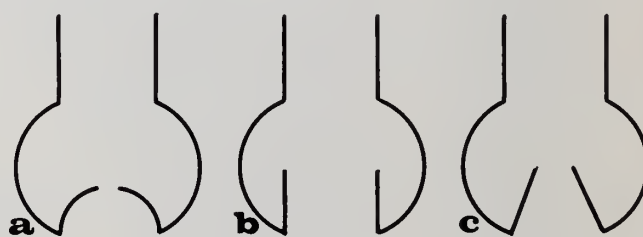


Figura 2. Diagrama ilustrando la configuración de la válvula aórtica en sístole:

- a) estenosis valvular: las valvas abren encorvadas formando una cúpula.
- b) válvula aórtica normal: las valvas abren por completo, quedando paralelas a la pared aórtica.
- c) estenosis sub-valvular: las valvas abren de forma incompleta.

Cuando los pacientes previamente asintomáticos con clínica de AS leve o moderada desarrollan síntomas (disnea al esfuerzo, dolor anginoso, etc.) se debe pensar en la presencia de una obstrucción severa. En pacientes con obstrucción severa pueden ocurrir episodios de síncope, una complicación muy seria de la AS, impidiendo que el ventrículo izquierdo aumente su débito cardíaco y que logre mantener un flujo cerebral adecuado durante el ejercicio.² La muerte súbita es otro peligro potencial en AS, con una incidencia variable de 1 a 19%.⁶ Los casos de muerte súbita en la serie anterior tenían en su mayoría obstrucciones severas y habían estado sintomáticos antes del accidente mortal.^{6, 7} La causa de muerte en estos pacientes se desconoce, aunque la mayoría cree que la presencia de disritmias ventriculares severas instigadas por una isquemia del miocardio, es el

mecanismo provocador más probable. Se postula también que un aumento súbito en la presión ventricular izquierda ocasiona un reflejo sincopal hipotensor que provoca isquemia y fibrilación ventricular.⁸

Es importante recordar que la estenosis aórtica suele ser una cardiopatía progresiva donde la aparición de síntomas, cambios auscultatorios y/o en las pruebas diagnósticas no-invasivas pueden anticipar una obstrucción severa. En ese caso se debe proceder inmediatamente a una evaluación detallada de la obstrucción por medio de un cateterismo cardíaco y cineangiocardiografía.

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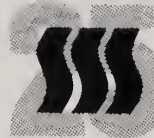
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Drug Interactions: MAO inhibitors may prolong and intensify the anticholinergic effects of antihistamines and the overall effects of sympathomimetic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed with 'Rynatan'.

Pregnancy Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Rynatan. It is also not known whether 'Rynatan' can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 'Rynatan' should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 'Rynatan' should not be administered to a nursing woman.

Adverse Reactions: Adverse effects associated with 'Rynatan' at recommended doses have been minimal. The most common have been drowsiness, sedation, dryness of mucous membranes, and gastrointestinal effects. Serious side effects with oral antihistamines or sympathomimetics have been rare.

Note: The following sections are optional and may be omitted.

Overdosage: *Signs & Symptoms*—may vary from CNS depression to stimulation (restlessness to convulsions). Antihistamine overdosage in young children may lead to convulsions and death. Atropine-like signs and symptoms may be prominent.

Treatment—Induce vomiting if it has not occurred spontaneously. Precautions must be taken against aspiration especially in infants, children and comatose patients. If gastric lavage is indicated, isotonic or half-isotonic saline solution is preferred. Stimulants should not be used. If hypotension is a problem, vasopressor agents may be considered.

Dosage and Administration: Administer the recommended dose every 12 hours.

Rynatan Tablets: Adults—1 or 2 tablets

Rynatan Pediatric Suspension: Children over six years of age—5 to 10 ml (1 to 2 teaspoonfuls); Children two to six years of age—2.5 to 5 ml (½ to 1 teaspoonful); Children under two years of age—Titrate dose individually.

How Supplied

Rynatan Tablets: buff, capsule-shaped, compressed tablets in bottles of 100 (NDC 0037-0713-92) and bottles of 500 (NDC 0037-0713-96)

Rynatan Pediatric Suspension: dark-pink with strawberry-currant flavor, in pint bottles (NDC-0037-0715-68)

Storage: 'Rynatan' Tablets—Store at room temperature; avoid excessive heat—(above 40°C/104°F).

Rynatan Pediatric Suspension—Store at controlled room temperature—between 15°C–30°C (59°F–86°F); protect from freezing. Issued 1/82



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Read this like your life depends on it.

Breast cancer found early and treated promptly has an excellent chance for cure. About a week after your period, practice this self-examination.



1. In bath or shower.

Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.

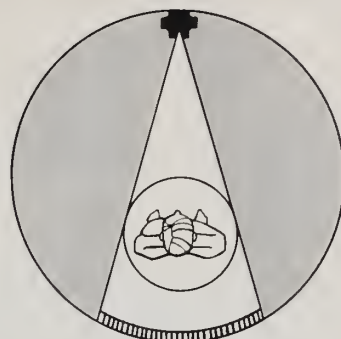


3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.



CT Diagnosis



Heriberto Pagán-Saez, MD.*

A 12 years old female developed severe headache with disorientation and loss of consciousness while at school. The CT scan with contrast material is shown in figure 1.

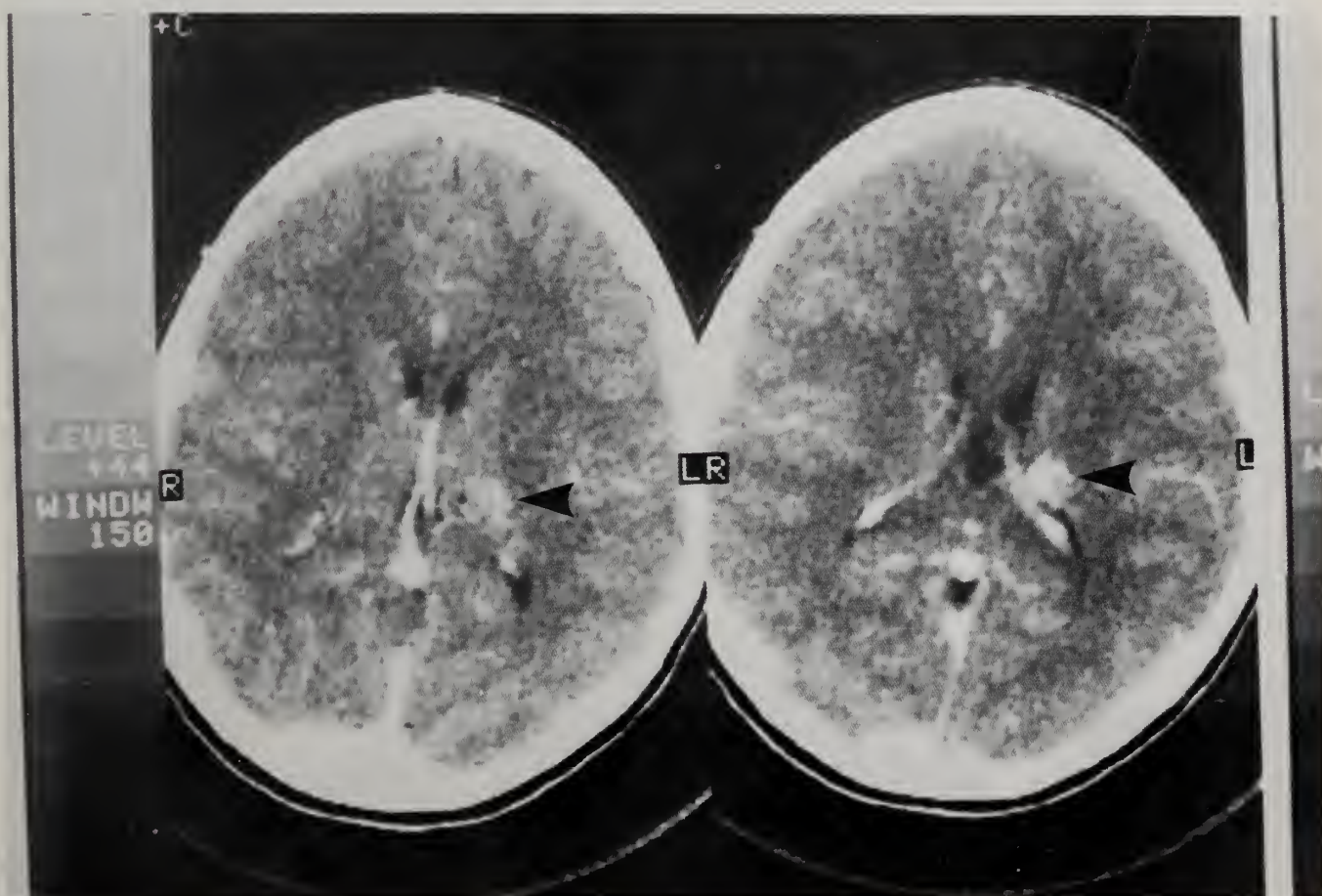


Figure 1. Scan after intravenous contrast shows an abnormal enhancing lesion located in the left paraventricular (see arrows)

What is your diagnosis?

*Director Department of Radiological Sciences University of Puerto Rico, Medical Sciences Campus, Río Piedras, Puerto Rico

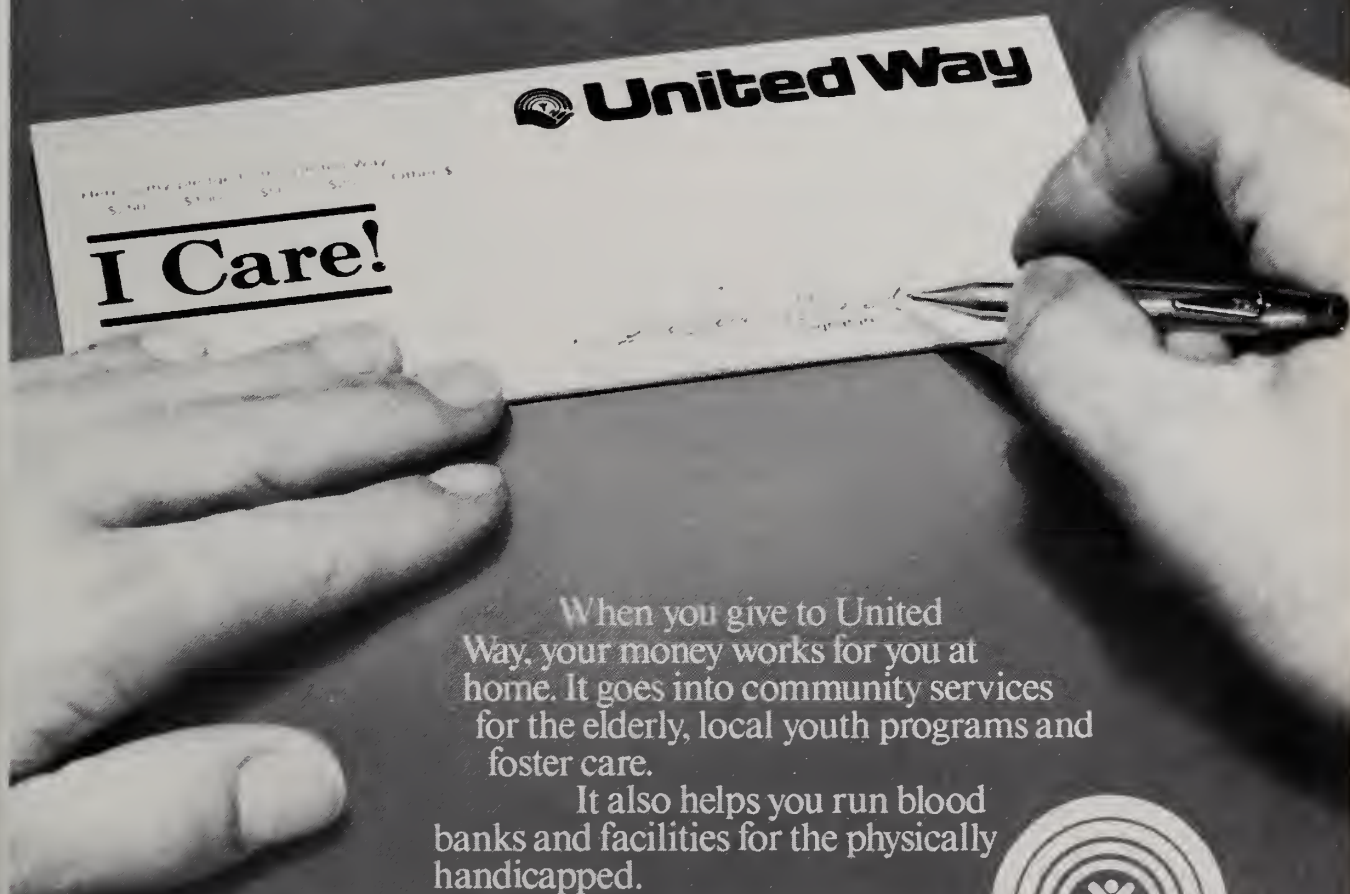
DIAGNOSIS:

ARTERIOVENOUS MALFORMATION



Figure 2. Blow up shows a large vein (arrow) draining into the galenic system and abnormally dilated vessels within the malformation (small arrows)

BUILD A BETTER COMMUNITY WITH YOUR BARE HANDS.



When you give to United Way, your money works for you at home. It goes into community services for the elderly, local youth programs and foster care.

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So when your United Way volunteer comes around, be generous.

A better community is in your hands.



United Way
THANKS TO YOU IT WORKS
FOR ALL OF US.

**On nitrates,
but angina still
strikes...**



After a nitrate, add ISOPTIN[®] (verapamil HCl/Knoll)

**To protect your patients, as well as their quality of life,
add Isoptin instead of a beta blocker.**

First, Isoptin not only reduces myocardial oxygen demand by reducing peripheral resistance, but also increases coronary perfusion by preventing coronary vasospasm and dilating coronary arteries — both normal and stenotic. These are antianginal actions that no beta blocker can provide.

Second, Isoptin spares patients the beta-blocker side effects that may compromise the quality of life.

With Isoptin, fatigue, bradycardia and mental depression are rare. Unlike beta blockers, Isoptin can safely be given to patients with asthma, COPD, diabetes or peripheral vascular disease. Serious adverse reactions with Isoptin are rare at recommended doses; the single most common side effect is constipation (6.3%).

Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin... for more comprehensive antianginal protection without side effects which may cramp an active life style.



**ISOPTIN. Added
antianginal protection
without beta-blocker
side effects.**

ISOPTIN[®] TABLETS

(verapamil HCl/Knoll)
80 mg and 120 mg

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN.

Precautions: ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients.

How Supplied: ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068



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2195

TRUTH

When the North Atlantic Treaty Organization was formed in 1949, it was formed for one reason. To stop Soviet aggression in Europe.

TRUTH

The Warsaw Pact's conventional fighting capabilities far exceed that of European NATO forces.

TRUTH

In order to maintain peace and freedom in Europe, NATO has effectively maintained a policy of deterrence with the Soviet Union.

TRUTH

The past 35 years of peace have been one of the longest periods of European peace in recorded history.

TRUTH

The Soviets will not risk war. Unless they are sure they can win.

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In recent comparative studies...

UNSURE

For relief of acute
musculoskeletal discomfort¹

SOMA^{®*} Tablets
(carisoprodol, 350 mg)

VS.

Valium^{®†}
(diazepam)

Mt. McKinley, located in Alaska,
is the highest mountain in
the United States. Its elevation
is 20,320 feet.

**In a double-blind study, at the end of
a seven-day course of therapy...¹**

Soma[®] (350 mg Q.I.D.) was found superior
to Valium^{®†} (5 mg Q.I.D.) in these three
important parameters: muscle spasm, mobil-
ity and overall relief ($p \leq 0.05$).

No significant differences were reported in
relieving pain or in improving sleep.

^{*}As an adjunct to rest, physical therapy and other
measures for the relief of discomfort associated with
acute, painful musculoskeletal conditions.

[†]Valium[®] is a registered trademark of Roche Products Inc.



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PASSED

For relief of acute
musculoskeletal discomfort²

SOMA^{®*} Tablets
(carisoprodol, 350 mg)

VS.

Flexeril^{®‡}
(cyclobenzaprine HCl)

**Another double-blind study, using
similar methodology, found...²**

Soma[®] (350 mg Q.I.D.) and Flexeril^{®‡}
(10 mg Q.I.D.) both effective:

- No statistically significant differences
between treatments.
- Flexeril had a statistically significant higher
incidence of dry mouth ($p \leq 0.05$).

**As Soma relieves muscle spasm,
activity impairment diminishes and
patients are often able to resume
more normal activities.**

References: 1. Boyles WF, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions: thoracolumbar strain or sprain. *Today's Therapeutic Trends*, vol. 1(1), 1983. A controlled double-blind study of 71 patients. 2. Rollings HE, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions—thoracolumbar strain or sprain: A double-blind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. *Curr Ther Res*, vol. 34, Dec. 1983. A controlled double-blind study of 58 patients.

*As an adjunct to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.

‡Flexeril[®] is a registered trademark of Merck Sharp & Dohme.

For prescribing information, please see next page.

Soma® (carisoprodol)

Before prescribing 'Soma', consult package circular or latest PDR Information, a brief summary of which follows:

INDICATIONS: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS: Porphyrin; allergy or idiosyncrasy to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

WARNINGS: *Idiosyncratic Reactions:* have appeared very rarely within minutes or hours after the first dose of carisoprodol. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation. Symptoms usually subside in several hours, but supportive and symptomatic therapy, including hospitalization, may be necessary.

Pregnancy and Lactation: Safe use has not been established; weigh potential benefits against potential hazards during pregnancy and lactation or in women of childbearing potential.

Usage in Children: 'Soma' — Not recommended under age 12.

Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g., driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive.

Drug Dependence: Use caution in addiction-prone patients.

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of carisoprodol.

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances.

Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock.

DOSAGE AND ADMINISTRATION: *Adults* — One 350 mg tablet 3 times daily and at bedtime.

OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used successfully with related drug, meprobamate.

HOW SUPPLIED: White, 350 mg tablets in bottles of 100 (NDC 0037-2001-01) and 500 (NDC 0037-2001-03).

Now available

SOMA[®] COMPOUND

Tablets (carisoprodol 200 mg + aspirin 325 mg)

Rx
Soma
Compound
Disp. as written

SOMA[®] COMPOUND with CODEINE[®]

Tablets (carisoprodol 200 mg + aspirin 325 mg + codeine phosphate 16 mg—
Warning: May be habit-forming)

Rx
Soma
Compound
with Codeine



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Hugh D. Allen, M.D., F.A.C.C.

He was studied with the Honeywell (Biosound Corp. Indianapolis, Ind) pulsed Doppler and Irex (Ramsey, NJ) continuous wave echocardiographs. Calculations were performed with an Apple II Plus computer (Cupertino, CA) and a prepared dedicated software program (Biodata, Davis, CA).



1. What is the Doppler echocardiographic diagnosis and its severity?
2. What are the Doppler characteristic of this lesion?
3. What is the differential diagnosis?

****University of Arizona Health Sciences Center Pediatric Cardiology, Tucson, AZ**

Answers

Aortic Regurgitation (AR).

Figure 1. Irex Continuous Wave (CW) tracing obtained from the suprasternal notch. Ascending aorta (AAo).

Systolic positive flow toward the transducer - Total forward flow (TFF).

Peak velocity (V) = 3 M/S, mean V = 70 cm/S.

Diastolic negative regurgitant flow (RF) away from transducer.

Mean V = 41 cm/S.

Figure 2. Same. Descending aorta (DAo).

Systolic negative flow away from transducer (TFF).

Peak V = 3 M/S, mean 92 cm/S.

Diastolic positive flow (RF) toward the transducer.

Mean V = 58 cm/S. Aorta dimension 2.69 cm.

TFF - RF should equal net forward flow (NFF), such as pulmonary artery (PA) flow; if not, the velocity may have been measured in a jet.

Figure 3. Honeywell Pulsed Doppler of PA flow, obtained by 2-D echo placement of sample volume (SV). See insert in left upper portion of the freeze-frame illustration.

Peak V = 1 M/S, mean 23 cm/S. PA diameter 2.53 cm. Flow = 6900 cc/min. Time-to-Peak Velocity (TPV) or Acceleration Time = 140 mS, which is normal.

Discussion

Doppler echocardiography of AR may reveal the following, with the SV in the left ventricular outflow tract (LVOT) or aorta (AAo, DAo): Apical- 5 or 2-chamber views, suprasternal, subcostal, left parasternal long and short axis, right parasternal:

- 1) a high velocity, harsh, rasping turbulent, broad banded diastolic flow, starting early in diastole and decreasing throughout diastole; may produce aliasing.
- 2) From suprasternal notch- diastolic negative flow below the baseline. From apical views a positive flow at the LVOT.
- 3) the AAo systolic flow shows spectral broadening/turbulence and increased peak V (even in absence of aortic stenosis), with an early onset.
- 4) severity of AR graded by: a) planimetry or digitization of areas under systolic and diastolic flow tracings from the aorta; RFr; RF in respect to TFF; use systolic volume flow from a second location, i.e., PA, diastolic mitral valve; b) left ventricular upstream flow mapping by range-gated pulsed Doppler: LVOT, body, apex, above, at or below mitral valve-RF distribution; c) downstream aortic level grading from distal transverse aorta; % regurgitation; d) regurgitant aortic valvular area/ aortic valvular orifice area ration or body surface area with 2-D echo.

In AR, Doppler echocardiography demonstrated high sensitivity, specificity and predictive value, and correlation with angiography. It was more useful than auscultation or echocardiography for detection of mild AR, and AR in the presence of mitral stenosis. It was better than

auscultation and echocardiography for valvular regurgitation- detection and severity.

AR by Doppler must be differentiated from: 1) artifacts- of transient high amplitude in early and mid diastole by inclusion of the ventricular septum in the SV, and initial valve motion artifacts by inclusion of the anterior mitral leaflet in the SV; 2) mitral stenosis (SV in mitral orifice) which produces a turbulent, high frequency, sustained diastolic flow in the left ventricular inflow tract; this signal may begin later in diastole than that of AR; 3) mitral prosthesis causing a high velocity jet; 4) decreased cardiac output; 5) the normal aortic diastolic run-off into the coronary arteries and sinuses of Valsalva.

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ARMY RESERVE. BE ALL YOU CAN BE.

What can you do for hypertensives like these?

On cimetidine

Impotent

Childhood
asthmatic

CNS
problems

Heavy
smoker

Diabetic

Patient descriptions are hypothetical composites based on clinical experience and evaluation of data.

Rely on one-tablet-a-day for these and virtually

Laura K is depressed ... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN® (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits ... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma.¹ Smoking has been implicated—especially in males.² Cardioselective TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This preference is not absolute.

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence.

Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³

At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.⁴

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen.

Unlike propranolol, cardioselective TENORMIN can reduce the likelihood of bronchospasm in susceptible patients.^{5,6}



dosage and cardioselectivity* all your hypertensives.

*Newly diagnosed...
workup shows
162/100 mmHg. On
cimetidine for pep-
tic ulcer. Don S
hates the thought
of yet another
medication.*

TENORMIN is not
metabolized by the
liver. Its pharmaco-
kinetics are unaf-
fected when it is
administered con-
comitantly with
cimetidine^{7,8} or
ranitidine.⁹



"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹⁰



*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

ONE TABLET A DAY
TENORMIN[®]
(atenolol)

See following page for brief summary of prescribing information.



STUART PHARMACEUTICALS

ONE TABLET A DAY TENORMIN® (atenolol)

Therapy
for virtually every
hypertensive
patient in your
practice.



TENORMIN® (atenolol)

A beta₁-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol) with caution—see OVERDOSAGE. Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg i.v.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min. 1.73 m² (normal range is 100-150 ml/min/1.73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1.73 m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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ASOCIACION MEDICA DE PUERTO RICO

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

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The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

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An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

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These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should be abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

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Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

*The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

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References: 1. Kales J et al: *Clin Pharmacol Ther* 12:691-697, Jul-Aug 1971. 2. Kales A et al: *Clin Pharmacol Ther* 18:356-363, Sep 1975. 3. Kales A et al: *Clin Pharmacol Ther* 19:576-583, May 1976. 4. Kales A et al: *Clin Pharmacol Ther* 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc* 27:541-546, Dec 1979. 6. Kales A, Kales JD: *J Clin Pharmacol* 3:140-150, Apr 1983. 7. Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther* 21:355-361, Mar 1977. 8. Zimmerman AM: *Curr Ther Res* 13:18-22, Jan 1971. 9. Amrein R et al: *Drugs Exp Clin Res* 9(1):85-99, 1983. 10. Monti JM: *Methods Find Exp Clin Pharmacol* 3:303-326, May 1981. 11. Greenblatt DJ et al: *Sleep* 5(Suppl 1):S18-S27, 1982. 12. Kales A et al: *Pharmacology* 26:121-137, 1983.

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